

Utility of Performing Routine Screening Tests of Infections in the Clinical Management of Preterm Labor in a Tertiary Hospital in the Philippines

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ABSTRACT

Objective. Preterm birth is a major cause of complications leading to death of children under 5 years old. Infections are important to be identified because antimicrobial treatment may prevent or delay progression to preterm delivery. This study determined if routine screening tests of infections are useful in the clinical management of preterm labor.

Methods. A cross-sectional (descriptive) study was done involving 417 pregnant patients who had preterm labor and was subsequently admitted from 2015 to 2019 at a tertiary hospital in the Philippines, using review of past medical records, inpatient charts, and admission charts.

Results. Majority of the patients delivered at less than 34 weeks, most of the culture results turned out negative, and urine tests were more commonly employed as screening tests for preterm labor. The endocervical and rectovaginal swab studies had no significant growths. Asymptomatic bacteriuria was diagnosed in 1 out of 10 patients and they were subsequently started on antibiotic treatment. Majority of the patients who were given antibiotics delivered within 48 hours from admission.

Conclusion. The routine use of cultures in the assessment of preterm labor is costly and is unlikely to be helpful in the clinical management of patients in preterm labor.

Keywords: screening tests, infections, management, preterm labor

INTRODUCTION

Preterm delivery is defined as any delivery of a newborn before 37 completed weeks. Worldwide, preterm birth affects 11% of births, with an estimated 15 million babies born prematurely every year.^{1,2} Complications surrounding preterm birth are the leading cause of death among children under 5 years of age.² Most preterm birth occurs in South Africa and South Asia, which is about 60% of the global burden. In the Philippines, there are about 350,000 preterm births per year, ranking eighth in the world.²

In 2002, Gonçalves and colleagues reported that intra-amniotic infection is considered as the primary cause of preterm labor in 25 to 40% of pregnancies with intact membranes and a third of cases with preterm prelabor rupture of membranes (PPROM).³ They theorized that once the infectious cause of a patient in preterm labor was identified, antimicrobial treatment may prevent its progression to preterm birth.

The researchers observed that screening tests for infection are routinely done among pregnant women in preterm labor in order to investigate the cause of preterm



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labor in a tertiary, public hospital in the Philippines. These tests are the following: urinalysis, urine Gram stain, culture, and sensitivity, rectovaginal swab Gram stain, culture, and sensitivity, and endocervical swab Gram stain, culture, and sensitivity. Antimicrobials are given to patients with preterm premature rupture of membranes starting at 24 weeks as group B-beta streptococcus (GBS) prophylaxis and to prolong latency. Tocolytics, commonly oral nifedipine, are given to patients in preterm labor usually for administration or completion of corticosteroids for lung maturity, and those who will benefit from delaying delivery (i.e., not in advanced labor, no intra-amniotic infection). Magnesium sulfate is given for neuroprotection when birth is anticipated among pregnant patients less than 32 weeks age of gestation.

It is unsure whether the results of these routine infectious screening tests played a significant role in the clinical management of the preterm labor in the inpatient setting. Currently, there are no studies which determine the prevalence of positive screening tests and its utility among women admitted for preterm labor in the Philippines. There is no local protocol indicating the utility of sending cultures to investigate the cause of preterm labor in this patient population. This will be the first study which aims to determine the utility of routine infectious screening tests in the clinical management of women admitted for preterm labor in a tertiary hospital in the Philippines. The results of this study will help in formulating local recommendations for the management of patients in preterm labor, and in providing guidelines in better allocation of our limited hospital resources.

MATERIALS AND METHODS

The institutional research ethics board reviewed and approved this 5-year cross-sectional (descriptive) study of women with singleton pregnancies who had preterm labor and was subsequently admitted from January 2015 to December 2019 at a tertiary hospital in the Philippines, using review of past medical records, inpatient charts, and admission charts of patients admitted for preterm labor. The charts were retrieved after approval of the hospital director thru the chief of the Medical Records Division. All patients' information were confidential and stored in a password-protected file, only accessible to the research investigators, research assistant, and statistician. It was disposed after a year from completion of the study. The costs of each test were obtained from the cashier's office of the hospital.

Patients were identified through a logbook of masterlist of admissions. Those who were included in the study were patients admitted for preterm labor with a live, singleton pregnancy between 24 weeks and 33 6/7 weeks. Information from the earliest admission of a patient and only the most recent pregnancy of a patient were included. Exclusion criteria were multifetal gestation, those with medical co-morbidities predisposing to preterm labor, known fetal anomalies,

hydramnios, indicated preterm birth, and unknown delivery outcome.

There were a total of 417 patients included in this study. Data were collected and encoded using Microsoft Excel. The prevalence of positive screening tests were determined. The frequency by which the routine screening tests incurred a change in the management were described. Continuous variables were reported as mean with standard deviation. The Mantel-Haenszel chi-squared test or Fisher's exact test were performed to determine the association between categorical variables. Pearson chi-square and Poisson regression were used to evaluate the significance of associations between tests results and preterm delivery, and to control for confounders.

RESULTS

A total of 417 women at 24 weeks to 33 weeks and 6 days age of gestation in preterm labor consulting at the emergency room and subsequently admitted were included in the study (Table 1). The average age of women in this cohort was 23 years old. Majority of these women were single (81.53%), unemployed (66.19%), and finished high school (58.51%). They had an average of four prenatal visits, with the most common prenatal consult done at the local health center (71.99%), followed by government institutions (21.85%), then by private physicians (6.16%). There were 35 patients who reported alcohol drinking during pregnancy (8.39%), 27 patients who smoked cigarettes (6.47%), and one patient who had illicit drug use (0.24%). Regarding obstetric history, the majority of women in the study population had two previous pregnancies and one livebirth. The average interpregnancy interval was three years and there were 15.59% (65/417) patients who had a history of prior preterm birth. There were only two patients (0.48%) who had a history of genitourinary infection.

As shown in Table 2, urinalysis was the most common screening test done (95%), followed by urine gram stain, culture, and sensitivity (urine GS/CS) (86.3%), rectovaginal swab gram stain, culture, and sensitivity (RVS GS/CS) (61.6%), and endocervical swab gram stain, culture, and sensitivity (ECC GS/CS) (19.4%). The prevalence of a positive urinalysis in our patient population was 56.8% (225/396). Meanwhile, the prevalence of a positive urine culture result was 2.8% (10/360). There was no significant growth among the endocervical and rectovaginal swab studies sent.

The clinical characteristics of patients included in our study are shown in Table 3. The average size of cervical dilatation upon admission was 5 centimeters. Majority (91.85%) of the patients delivered at less than 34 weeks. Only 8.15% delivered at 34 weeks or more. Those who had preterm birth less than 34 weeks had a significantly higher value of cervical dilatation at an average of 5 centimeters cervical dilatation on admission, compared to those who delivered at 34 weeks or more who had an average cervical dilatation of 2 centimeters. Urinalysis was more commonly

Table 1. Socio-demographic and Obstetric Characteristics of the Population

Characteristics	Overall	PTB* <34	PTB* ≥34	p-value
Frequency	417 (100%)	383 (91.85%)	34 (8.15%)	-
Age in years	23 (19, 29)	23 (19, 29)	24 (20, 31)	0.74
Marital status				
Single	340 (81.53%)	314 (81.98%)	26 (76.47%)	
Married	76 (18.23%)	68 (17.75%)	8 (23.53%)	0.67
Widowed	1 (0.24%)	1 (0.26%)	-	
Occupation				
Unemployed	276 (66.19%)	258 (67.36%)	18 (52.94%)	
Employed	98 (23.50%)	89 (23.24%)	9 (26.47%)	0.10
Others	43 (10.31%)	36 (9.40%)	7 (20.59%)	
Educational attainment				
Elementary	37 (8.87%)	34 (8.88%)	3 (8.82%)	
High school	244 (58.51%)	223 (58.22%)	21 (61.76%)	0.94
Vocational	36 (8.63%)	34 (8.88%)	2 (5.88%)	
College	100 (23.98%)	92 (24.02%)	8 (23.53%)	
Number of prenatal visits	4 (2, 6)	4 (2, 6)	5 (4, 7)	0.01*
Location of prenatal visits				
Local health center	257 (71.99%)	235 (72.09%)	22 (70.97%)	
Government institution	78 (21.85%)	70 (21.47%)	8 (25.81%)	0.70
Private institution	22 (6.16%)	21 (6.44%)	1 (3.23%)	
Vices				
Cigarette smoking	27 (6.47%)	25 (6.53%)	2 (5.88%)	0.84
Alcohol drinking	35 (8.39%)	33 (8.62%)	2 (5.88%)	0.55
Use of illicit drugs	1 (0.24%)	-	1 (2.94%)	0.08
Obstetric history				
Number of pregnancies	2 (1, 3)	2 (1, 3)	2 (1, 3)	0.78
Number of livebirths	1 (0, 2)	1 (0, 2)	1 (0, 1)	0.59
Inter-pregnancy interval	3 (1, 5)	3 (2, 5)	2 (1, 6)	0.56
History of preterm birth	65 (15.59%)	59 (15.40%)	6 (17.65%)	0.73
History of genito-urinary infection	2 (0.48%)	2 (0.52%)	-	0.61

*PTB, preterm birth

Table 2. Prevalence of Positive Screening Tests in Preterm Labor Cohort

Screening Test	Patients Screened	Screened (95% CI)	Positive Tests	Prevalence (95% CI)
Routine urinalysis	396/417	95% (92.4-96.9%)	225/396	56.8% (51.8-61.8%)
Urine GS/CS*	360/417	86.3% (82.7-89.5%)	10/360	2.8% (1.3-5%)
Endocervical swab	81/417	19.4% (15.7-23.6%)	0/81	-
Rectovaginal swab	257/417	61.6% (56.8-66.3%)	0/257	-

*GS/CS, gram stain, culture and sensitivity

done among patients who delivered at less than 34 weeks (95.30%) compared to 91.18% of patients who delivered at 34 weeks or more. Urine culture (94.12% versus 85.64%), endocervical studies (52.94% versus 16.45%), and rectovaginal studies (79.41% versus 60.05%) were more common among patients who delivered at 34 weeks or more. The interval from submission of the diagnostic test to release of result took one to two days.

Among patients who had preterm birth at less than 34 weeks and had positive urinalysis results, 10.18% (39/383) of patients received treatment while 43.08% did not receive treatment (Table 3). In patients who delivered at least 34

weeks and more and had positive urinalysis results, 14.71% (5/34) of patients received treatment while 47.16% did not receive treatment. Moreover, among patients who had preterm birth less than 34 weeks and had positive urine culture results, six out of 383 patients (1.57%) received treatment while one patient (0.26%) did not receive treatment. In patients who delivered at least 34 weeks and more and had positive urine culture results, three out of 34 patients (8.82%) received treatment.

As shown in Table 4, patients who had preterm birth at 34 weeks or more had higher proportion of being given corticosteroids, empiric antibiotics, definitive antibiotics,

Table 3. Clinical Characteristics of the Population

Characteristics	Overall	PTB* <34	PTB* ≥34	p-value
Frequency	417 (100%)	383 (91.85%)	34 (8.15%)	-
Size of cervical dilatation on admission	5 (3, 9)	5 (3, 10)	2 (1, 3)	<0.01*
Urinalysis				
Not done	21 (5.04%)	18 (4.70%)	3 (8.82%)	
Done	396 (94.96%)	365 (95.30%)	31 (91.18%)	
Negative	171 (41.01%)	161 (42.04%)	10 (29.41%)	0.39
Positive	225 (53.96%)	204 (53.26%)	21 (61.76%)	
No treatment	181 (43.41%)	165 (43.08%)	16 (47.16%)	
With treatment	44 (10.55%)	39 (10.18%)	5 (14.71%)	
Urine culture studies				
Not done	57 (13.67%)	55 (14.36%)	2 (5.88%)	
Done	360 (86.33%)	328 (85.64%)	32 (94.12%)	
Not available	40 (9.59%)	36 (9.40%)	4 (11.76%)	
Negative	310 (74.34%)	285 (74.41%)	25 (73.53%)	0.05*
Positive	10 (2.40%)	7 (1.83%)	3 (8.82%)	
No treatment	1 (0.24%)	1 (0.26%)	-	
With treatment	9 (2.16%)	6 (1.57%)	3 (8.82%)	
Endocervical studies				
Not done	336 (80.58%)	320 (83.55%)	16 (17.06%)	
Done	81 (19.42%)	63 (16.45%)	18 (52.94%)	
Not available	10 (2.40%)	9 (2.35%)	1 (2.94%)	<0.01*
Negative	71 (17.03%)	54 (14.10%)	17 (50%)	
Positive / no treatment	0	-	-	
Positive / with treatment	0	-	-	
Rectovaginal studies				
Not done	160 (38.37%)	153 (39.95%)	7 (20.59%)	
Done	257 (61.63%)	230 (60.05%)	27 (79.41%)	
Not available	9 (2.16%)	8 (2.09%)	1 (2.94%)	0.08
Negative	248 (59.47%)	222 (57.96%)	26 (76.47%)	
Positive / no treatment	0	-	-	
Positive / with treatment	0	-	-	
Interval to results				
Urine culture studies	2 (1, 2)	2 (1, 2)	2 (1, 2)	0.69
Endocervical studies	2 (1, 2)	2 (1, 2)	2 (1, 2)	0.70
Rectovaginal studies	1 (1, 2)	1 (1, 2)	1 (1, 2)	0.55

*PTB, preterm birth

tocolytics, and micronized progesterone (82.35% versus 51.17%, 29.41% versus 21.67%, 11.76% versus 1.31%, 79.41% versus 32.28%, and 35.29% versus 2.09%, respectively). On the other hand, those with preterm birth less than 34 weeks have significantly lower values of pediatric aging (33 weeks versus 35 weeks), thus a higher proportion of neonates requiring neonatal intensive care unit (NICU) admission (64.49% versus 32.35%), than otherwise. Male neonates were more common among those who delivered less than 34 weeks (53.52%) while there were more female neonates among those who delivered at 34 weeks or more (58.82%).

Among the patients who had antibiotic therapy, 9.6% (9/94) had positive urine culture results. Five out of 9 patients continued the initial empiric antibiotics since it was found to be sensitive to the causative organism, while 3 patients had a shift in antibiotics based on the sensitivity result. There was

1 patient who was only started on antibiotic therapy after knowing the positive urine culture result. It can be noted that less than a quarter of patients who received antibiotics had prolonged interval to delivery beyond 48 hours from admission (19/94, 20.2%, CI: 12.6–29.8%). The most common indication for antibiotic use was asymptomatic bacteriuria (36/94, 38.3%), followed by bacteriuria on urinalysis (17/94, 18.1%). Two patients had acute pyelonephritis while 1 patient had acute cystitis.

The screening tests that were done but which results were not available ranges from 3.5–12.35%. These tests cost PhP 48,400. The urinalysis results which were available and positive (56.82%) cost PhP 54,000. It is only 24% (PhP 13,000) more costly than the total amount of negative results. The urine culture results which were available and positive (2.78%) cost PhP 7,350. The total cost paid for the negative

Table 4. Therapeutics and Clinical Outcomes in the Population

Outcomes	Overall	PTB* <34	PTB* ≥34	p-value
Frequency	417 (100%)	383 (91.85%)	34 (8.15%)	-
Therapeutic management				
Antenatal corticosteroids	224 (53.72%)	196 (51.17%)	28 (82.35%)	<0.01*
Empirical antibiotics	93 (22.30%)	83 (21.67%)	10 (29.41%)	
Definitive antibiotics	9 (2.16%)	5 (1.31%)	4 (11.76%)	0.01*
Tocolytic agents	151 (36.21%)	124 (32.38%)	27 (79.41%)	<0.01*
Micronized progesterone	20 (4.80%)	8 (2.09%)	12 (35.29%)	0.01*
Disposition				
Direct rooming-in (DRI)	159 (38.13%)	130 (33.94%)	29 (85.29%)	
Neonatal intensive care unit (NICU)	258 (61.87%)	247 (64.49%)	11 (32.35%)	
Pediatric aging	33 (31, 35)	33 (31, 35)	35 (35, 36)	<0.01*
Sex of the neonate				
Female	198 (47.48%)	178 (46.48%)	20 (58.82%)	0.16
Male	219 (52.52%)	205 (53.52%)	14 (41.18%)	

*PTB, preterm birth

Table 5. Diagnostic Tests and Corresponding Costs

Diagnostic Tests	Urinalysis (N=396)	Cost (PhP 240)	Urine GS/CS* (N=360)	Cost (PhP 735)	ECS GS/CS* (N=81)	Cost (PhP 1000)	RVS GS/CS* (N=257)	Cost (PhP 1000)	Total
Not available	-		40 (11.11%)	29,400	10 (12.35%)	10,000	9 (3.50%)	9,000	48,400
Available but negative	171 (43.18%)	41,040	310 (86.11%)	227,850	71 (87.65%)	71,000	248 (96.50%)	248,000	587,890
Available and positive	225 (56.82%)	54,000	10 (2.78%)	7,350	0		0		61,350
Total		95,040		264,600			81,000		257,000 697,640

*GS/CS, gram stain, culture and sensitivity

urine culture results were PhP 227,850. Meanwhile, the available endocervical swab (87.65%) and rectovaginal swab studies (96.50%) all have negative results, which cost PhP 71,000 and PhP 248,000, respectively. These are shown in Table 5.

DISCUSSION

There are various socio-demographic and clinical characteristics among pregnant patients that can be linked to increased risks of preterm birth. The women included in this study were on average 23 years old, already had two previous pregnancies, and at least one livebirth. These factors may imply that they had younger age of first childbirth which is a known contributing factor to preterm birth.⁴ The average interpregnancy interval of three years that was found in this study agrees to the findings of Shachar et al. that interpregnancy interval of more than three years after a livebirth was at increased odds of preterm delivery.⁵ Patients that are within this subgroup may benefit from interventions that reduce preterm birth. However, since the population size seemed to be small, it was not statistically significant.

Most of the patients in this study were single, unemployed, and achieved high school as their educational attainment. Comparable to published literature, these factors are known to be associated with increased risk for preterm birth.⁶⁻⁸ The prevalence of smoking during pregnancy in this

study is higher compared to the latest global prevalence of 1.7%.⁹ The prevalence of alcohol consumption and illicit drug use during pregnancy were slightly lower than the global prevalence of 9.8% and 1.65%, respectively.^{10,11} This implies that preconceptual counseling should include surveying for these vices and counseling patients and their partners on its negative effects during pregnancy.

In this study, urine tests were more commonly utilized over swab studies and was statistically significant ($p<0.01$). In contrast with the study of Bastek et al., the percentage of patients screened with both urine and swab tests were high at 71.75-81.5%.¹² Meanwhile, the prevalence of a positive urine culture test, which was 2.8%, was within the lower range of published global prevalence, which are 1.2-35%, but lower compared to local prevalence noted by Sescon et al. in 2003, which was 4.3%.¹²⁻¹⁶ Notably, there was no significant growth of organisms found in all of the endocervical and rectovaginal swab studies sent. This can be attributed to the low prevalence of sexually transmitted infections and group B streptococcus in the Philippines.^{17,18} More importantly, there can be issues with specimen collection and transport system when endocervical and rectovaginal swabs are done. Based on the local clinical practice guidelines (CPG) on preterm labor and birth, for cervicitis, Nucleic Acid Amplification Tests (NAATs) are the screening tests that should be used to document subclinical infection.¹⁹ These are also the recommended tests by the United States' Centers

for Disease Control and Prevention (CDC) to detect *C. trachomatis* and *N. gonorrhoeae*.²⁰ However, these tests are not currently available in the tertiary hospital where the study was conducted.

Similar to the study by Bastek et al., those who delivered earlier at less than 34 weeks had a more advanced cervical dilatation versus those who delivered at 34 weeks or more.¹² It can be noted that since the patients in the group of preterm birth at 34 weeks or more were on the latent phase of labor, the complete battery of screening tests were able to be collected among them.

In this study, only 10.55% of patients with positive urinalysis were treated. In practice, when the white blood cell (WBC) count in the urinalysis of a centrifuged urine is at least 5 per high power field (HPF), and the patient has no symptoms, then asymptomatic bacteriuria (ASB) is considered. Antibiotic treatment is started. The basis of this is the local CPG on urinary tract infection published in 2004. However, it should be cleared that only if urine culture is not available, an initial Gram stain of centrifuged urine could be used, and if it is positive (or the same morphology of bacteria is seen in more than 6 of 12 HPFs in centrifuged urine sample), it must be followed by a urinalysis to determine pyuria. This is the time that a cut-off level of more than 5 WBCs per HPF in a urinalysis is used to diagnose ASB. In diagnosing ASB, urine culture should be prioritized over urinalysis, since the standard urine culture of clean-catch midstream urine is the test of choice in screening for ASB.²¹ This guideline has been updated in 2013, wherein it states that urinalysis is not anymore recommended as an initial screening test for ASB and reiterates that ASB in pregnancy is diagnosed with the presence of $>100,000$ CFU/mL of the same uropathogen in two consecutive midstream urine specimens or ≥ 100 CFU/mL of a single uropathogen in one catheterized urine specimen with absent urinary symptoms. It also recommended that one urine culture is an acceptable alternative for the diagnosis of ASB in pregnancy only in settings wherein obtaining two consecutive urine cultures is not feasible or is difficult.²²

Since most of the patients who had preterm birth at 34 weeks or more were in the latent phase of labor, they were provided with majority of the therapeutics, thus might contribute to the lower NICU admission. As with the study by Peelen et al., male neonates were more common among those with preterm birth less than 34 weeks and can be an important risk factor for preterm labor.²³

In this study, among the screening tests, results of urinalysis and urine culture studies affected the clinical management of women admitted for preterm labor. Only nine out of 94 patients (9.6%) who received empiric antibiotics, the urine culture eventually turned out positive. Among these, more than half continued the initial empiric treatment, a third had antibiotic shift, and only one was started treatment based on the urine culture result. Antibiotics were also started on 38.3% (36/94) for asymptomatic bacteriuria. Notably,

even if the urine culture was negative and WBC was less than 5/HPF on urinalysis, 18.1% (17/94) patients received antibiotics for elevated bacteria on urinalysis.

Majority (79.8%) of the patients who were given antibiotics delivered within 48 hours from admission. Less than a quarter of patients who received antibiotics had prolonged interval to delivery beyond 48 hours from admission (20.2%, CI: 12.6-29.8%). The efficacy of antibiotic treatment in prolonging the pregnancy of women in preterm labor with positive screening tests are difficult to determine due to the limitations of the study.

The tests that were done but were not available during chart review and probably did not affect management cost PhP 48,400. This could have been allotted in other aspects of healthcare. Majority (97.22%) of the urine cultures sent were negative. The cost of all the negative urine culture results was PhP 227,850. It agrees with the findings of Hundley et al. that the routine use of urine cultures in the assessment of preterm labor is costly.¹³ Except in the presence of specific complaints, Hundley et al. noted that it adds little value to obtaining a diagnosis.¹³ In this study, it was found that all endocervical and rectovaginal swab studies sent had no significant growth. If these studies were not sent, the savings could be PhP 319,000. This resource can be allocated in other aspects of the healthcare system in order to improve maternal and neonatal outcomes.

This study had limitations. The design employed in this study was retrospective and descriptive only. The completeness of case record entries was a limiting factor to the results of the study. The results of this study done among Filipino women might not be generalizable to other ethnicities. There is only a small number of positive urine culture tests, thus this study needs a larger population of patients to determine the efficacy of antibiotics in prolonging pregnancy among patients in preterm labor.

CONCLUSION

This study determined the utility of performing routine screening tests of infections in the clinical management of preterm labor in a tertiary hospital in the Philippines. These tests were the following: urinalysis, urine culture and sensitivity, rectovaginal swab culture and sensitivity, and endocervical swab culture and sensitivity. Based on this study, majority of the patients delivered at less than 34 weeks. Most of the culture results turned out negative. Urine tests were more commonly employed as screening tests for preterm labor. About 1 in 10 patients diagnosed with asymptomatic bacteriuria using routine urinalysis were started with antibiotic treatment. Only 2.8% of the urine culture tests turned positive. Among those who were already on antibiotics, 9.6% of the patients were guided by the urine culture sensitivity result. All the endocervical and rectovaginal swab studies sent had no significant growths. Majority of the patients who were given antibiotics delivered within 48 hours from admission. The

routine use of cultures in the assessment of preterm labor is costly and is unlikely to be helpful in the clinical management of patients in preterm labor.

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Statement Of Authorship

Both authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

Both authors declared no conflicts of interest.

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