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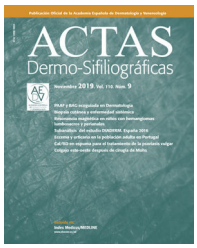

ORIGINAL ARTICLE

[Translated article] Adverse Drug Reactions Are the Main Causes of Erythroderma in an Argentinian Teaching Hospital: A Retrospective Study of 70 Patients☆

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KEYWORDS
Erythroderma;
Exfoliative dermatitis;
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Abstract
Background: Erythroderma, characterized by erythema and scaling that affects at least 90% of the body, has diverse causes. Most of the clinical manifestations and laboratory findings are nonspecific, making diagnosis challenging.
Material and methods: Retrospective study of patients treated between January 1, 2010, and June 1, 2020. We reviewed the records to identify all patients with erythroderma who were hospitalized in Hospital Italiano de Buenos Aires and followed for at least 6 months. We extracted information on clinical histories, the characteristics of the episodes, laboratory and histopathologic findings, and clinical course.
Results: Seventy patients were studied. The mean age at onset was 63 years, and the ratio of men to women was 1.2:1. Adverse drug reactions caused the largest proportion of the rashes (48%), and vancomycin was the most common culprit (involved in 30% of the cases). The next most frequent cause was a preexisting skin disease, psoriasis being the most common (in 42%). The clinicopathologic correlation was adequate for diagnosis after the first biopsy in 40% of patients, but the diagnostic yield increased to 76% with the second biopsy. The largest number of biopsies required was 8, in 2 patients. The outcome was favorable in 92% of the cases.
Conclusion: Adverse reactions to medications accounted for the largest proportion of erythroderma cases in this series, and vancomycin was the main culprit. We found no statistically significant associations among the variables studied. Nor did we identify potential predictors of causes, poor outcomes, or mortality.

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PALABRAS CLAVE
Eritrodermia;
Dermatitis exfoliativa;
Histopatología;
Fármacos

Las reacciones adversas a fármacos son la primera causa de eritrodermia. Estudio retrospectivo de 70 pacientes en un hospital universitario de Argentina

Resumen

Antecedentes: La eritrodermia es un cuadro caracterizado por un eritema y descamación que compromete al menos el 90% de la superficie corporal. Su etiología puede ser variable. La mayor parte de sus características clínicas y alteraciones del laboratorio son inespecíficas, lo que hace que el diagnóstico sea un desafío.

Materiales y métodos: Se realizó un estudio retrospectivo en el periodo comprendido entre el 1 de enero de 2010 y el 1 de junio de 2020. Se revisaron los antecedentes, las características clínicas, los hallazgos de laboratorio e histopatológicos, así como la evolución de todos los pacientes con una eritrodermia hospitalizados en el Hospital Italiano de Buenos Aires, con un seguimiento mínimo de 6 meses.

Resultados: Se incluyeron 70 pacientes. La edad media de aparición fue de 63 años con una relación hombre:mujer de 1,2:1. La principal causa de eritrodermia fueron las reacciones adversas a fármacos (48%), siendo la vancomicina el principal medicamento involucrado (30%), mientras que la segunda causa fueron las dermatosis preexistentes, dentro de las cuales la psoriasis fue la más común (42%). En el 40% de los pacientes se observó una adecuada correlación clínico-patológica con la primera biopsia, mientras que el rédito diagnóstico aumentó a un 76% con la segunda. El número máximo de biopsias requerido para efectuar el diagnóstico etiológico fue de 8 (2 pacientes). La evolución fue favorable en el 92% de los casos.

Conclusión: Las reacciones adversas a fármacos fueron la primera causa de eritrodermia y la vancomicina el fármaco responsable más frecuente. No se encontraron asociaciones estadísticamente significativas entre las variables estudiadas, ni se identificaron predictores de una determinada etiología, marcadores de mala evolución o factores de riesgo asociados a mortalidad.

Introduction

Erythroderma, or exfoliative dermatitis, is a rare condition characterized by erythema and scaling that affects more than 90% of the body; it has multiple causes.[1,2]

The pathophysiology of erythroderma is poorly understood and varies according to the underlying cause. Research to date has identified several triggers that induce massive recruitment of inflammatory cells to the skin. This recruitment accelerates skin cell turnover, causing the characteristic clinical manifestations of erythroderma and, in turn, a loss of proteins, fluids, electrolytes, and nucleic acids.[3]

Little has been published on the epidemiologic and clinical characteristics of erythroderma, or on causes, mortality, or factors associated with clinical course. The few studies that exist have been conducted in Europe and Asia and indicate that erythroderma is more common in male patients (male to female ratio, 3:1) and has a mean age of onset of 52 years in adults.[2–8] The most common causes identified are, by order of frequency, psoriasis, atopic dermatitis, contact dermatitis, adverse drug reactions (ADRs), pityriasis rubra pilaris, and lymphoproliferative disorders. In most studies, as many as 30% of cases are idiopathic.[4,5] Lifelong follow-up and age- and sex-appropriate tests are important, as there is evidence that patients with erythroderma may develop cutaneous T-cell lymphomas or solid tumors.[1,2]

A range of histopathologic findings have been described in erythroderma, but no correlations with cause have been established. Interpretation of histology findings is challenging, as features specific to underlying skin conditions are masked by the nonspecific changes observed in erythroderma. Multiple skin biopsies are sometimes necessary to reach a definitive diagnosis.

Patients with erythroderma may develop cardiovascular, renal, metabolic, or other complications, such as infections. Mortality rates range between 18% and 64% depending on the series.[5] Securing a firm, early diagnosis and initiating prompt, specific treatment is thus crucial.[1–5] The aim of this study was to describe the demographic and clinical characteristics of patients with erythroderma; examine causes, laboratory abnormalities, histopathologic findings, in-hospital complications, treatment, and clinical course; and investigate associations between study variables.

Materials and Methods

Study Design

Analytical observational study of a retrospective cohort of patients diagnosed with erythroderma at Hospital Italiano de Buenos Aires, a tertiary care hospital in Argentina.

Population

The cohort comprised consecutive adults (>18 years) with erythroderma who were evaluated by the dermatology

Table 1 Causes of Erythroderma and Time to Diagnosis.

Cause	% (no. of patients/total patients with erythroderma)	Median (IQR) time to diagnosis, *d*
Drugs	48.6 (34/70)	7 (0–30)
Psoriasis	20 (14/70)	5 (0–365)
Mycosis fungoides	5.7 (4/70)	25 (6–30)
Pityriasis rubra pilaris	4.3 (3/70)	12 (1–365)
Eczema	4.3 (3/70)	7 (6–160)
Sézary syndrome	4.3 (3/70)	30 (1–60)
Cutaneous T-cell lymphoma	2.9 (2/70)	5 (1–8)
Graft-vs-host disease	2.9 (2/70)	3 (1–4)
Blistering disease	2.9 (2/70)	5 (2–7)
Urticaria	1.4 (1/70)	–
Idiopathic	1.4 (1/70)	–
Paraneoplastic	1.4 (1/70)	–

Abbreviation: IQR, interquartile range.

department at Hospital Italiano de Buenas Aires between January 1, 2010 and June 1, 2020 and had at least 6 months of follow-up. All the patients were hospitalized when included in the cohort.

Exploratory Measures and Variables

We systematically reviewed the electronic medical records of all patients included. The following information was recorded in a purpose-designed database: personal data, medical and pharmacological history, previous episodes of erythroderma, onset (acute [appearance of skin lesions within 24–48 h] vs. insidious [gradual cephalocaudal spread, with lesions taking weeks or even months to fully develop]), duration, and laboratory findings. All patients underwent the following laboratory tests while hospitalized: complete blood count, blood glucose, liver and kidney function, serum proteins and lipids, lactate dehydrogenase, ionogram, serum uric acid test, and inflammatory markers. We also recorded histopathologic findings from skin biopsy pathology reports, treatments, outcomes, in-hospital complications, and relapses (yes/no). Deaths were grouped into 3 categories: deaths due to erythroderma (patients who died of erythroderma-related complications such as water–electrolyte imbalance, infection, and multiorgan failure), deaths due to pre-existing conditions (patients who died of an existing condition during follow-up, after resolution of the erythroderma), and deaths unrelated to erythroderma.

Statistical Analysis

Quantitative variables were tested using the Shapiro–Wilk test for normality. All the variables were nonnormally distributed and are therefore reported as median and interquartile range (IQR). Categorical variables are reported as absolute and relative frequencies. Associations were analyzed using the Fisher exact test for categorical variables and the Mann–Whitney *U* test for quantitative variables. Statistical significance was set at a *P* value of less than .05. The statistical analyses were performed in STATA (version 14.0).

The study was approved by the ethics committee at Hospital Italiano de Buenos Aires (Protocol No. 5693).

Results

The medical records of 83 patients with suspected erythroderma were reviewed; 70 patients met the inclusion criteria and were studied. Median follow-up was 1 year (range, 6 months to 10 years). Thirty-six patients (52%) were men, and the median age was 63 years (IQR, 48–74 years). Median age at onset of erythroderma was similar in men and women (62 vs. 60 years). Thirty patients had a pre-existing skin condition, the most common being psoriasis. Onset was acute in 53 patients (76%).

Adverse drug reactions (ADRs) were the cause of erythroderma in 34 patients (48%). The most common drug involved was vancomycin (8 patients), followed by lamotrigine (5 patients) and trimethoprim-sulfamethoxazole (4 patients). The other causes are shown in Table 1. Causes were similar in men and women.

All the patients had erythema and scaling. Additional skin manifestations included islands of normal skin (22 patients, 32%) and palmoplantar keratoderma (5 patients, 7%). Pruritus was the most common clinical finding (67 patients, 95%), followed by edema (18 patients, 25%), lymphadenopathy (17 patients, 24%), and fever (4 patients, 5.7%).

Skin biopsy was performed in all patients (within 48 h of hospitalization in 58 cases [83%]). The histopathologic findings are summarized in Table 2. Histopathologic features were useful for establishing a definitive diagnosis in 69 patients (98%). Median time to diagnosis was 7 days (range, 0–365 days). Patients diagnosed with cutaneous lymphoma, chronic eczema, and pityriasis rubra pilaris required more biopsies (between 6 and 8), and the median time to diagnosis in this group was 25 days (Table 1). Consecutive biopsies were performed in patients who required more than 1 biopsy; they were performed during flare-ups and were repeated over a maximum period of 1 year until a definitive diagnosis was reached. Just 1 biopsy was required to establish a diagnosis in patients with drug-induced erythroderma.

The diagnosis was modified in 7 patients during follow-up. The initial diagnosis had been based on histopathologic

Table 2 Histopathologic Findings in Patients with Erythroderma.

Histopathologic findings	ADR (n = 34)	Ps (n = 14)	CL (n = 9)	Eczema (n = 3)	PRP (n = 3)
Exocytosis of lymphocytes	34/34	5/14	9/9	2/3	0/3
Spongiosis	0/34	9/14	6/9	3/3	2/3
Eosinophilic infiltrate	34/34	8/14	0/9	0/3	1/3
Atypical lymphocytic infiltrates in the dermis	0/34	0/14	9/9	0/3	0/3
Necrotic keratinocytes	22/34	0/14	0/9	0/3	0/3
Acanthosis	0/34	14/14	5/9	3/3	3/3

Abbreviations: ADR, adverse drug reaction; CL, cutaneous lymphoma; PRP, pityriasis rubra pilaris; Ps, psoriasis.

Table 3 Laboratory Findings in Patients with Erythroderma.

Finding	% (no. of patients/total patients tested)	ADR	Ps	CL	Eczema	PRP	Other
Hyperglycemia (blood glucose > 140 mg/dL)	17 (12/70)	4/12	5/12	3/12	0/12	0/12	0/12
Anemia (hemoglobin < 10 g/dL)	19 (13/70)	10/13	1/13	1/13	0/13	0/13	1/13
Leukopenia (< 4000/mm^3)	14 (10/70)	5/10	0/10	2/10	1/10	0/10	2/10
Leukocytosis (> 11 000/mm^3)	36 (25/70)	14/25	4/25	3/25	1/25	1/25	3/25
Eosinophilia (> 500/mcL)	66 (46/70)	22/46	10/46	6/46	3/46	4/46	3/46
Low platelet count (> 11 000/mm^3)	27 (19/70)	9/19	2/19	4/19	0/19	0/19	4/19
Kidney failure (creatinine > 1.5 mg/dL)	20 (14/70)	8/14	3/14	1/14	1/14	0/14	1/14
Elevated transaminases	21 (15/70)	12/15	1/15	2/15	0/15	0/15	0/15
Lactate dehydrogenase (> 210 IU/L)	80 (28/35)	10/28	5/28	4/28	3/28	3/28	4/28
Hyponatremia (< 135 mmol/L)	23 (16/70)	10/16	2/16	1/16	1/16	0/16	2/16
Hypernatremia (< 135 mmol/L)	8 (4/52)	2/4	0/4	0/4	1/4	1/4	0/4
Hypophosphatemia (< 2.5 mg/dL)	29 (15/52)	8/15	1/15	0/15	1/15	2/15	3/15
Hyperphosphatemia (< 4.5 mg/dL)	7 (5/70)	2/5	1/5	1/5	0/5	0/5	1/5
Hypopotassemia (< 3.5 mmol/L)	9 (5/54)	2/5	1/5	2/5	0/5	0/5	0/5
Hypokalemia (< 8.5 mg/dL)	80 (27/34)	14/27	6/27	3/27	1/27	0/27	3/27
Erythrosedimentation (> 20 mm)	81 (21/26)	7/21	7/21	3/21	0/21	2/21	2/21
CRP (>10 mg/L)	81 (21/26)	10/21	6/21	1/21	0/21	2/21	2/21
Hypoproteinemia (< 6 g/dL)	71 (50/70)	27/50	9/50	6/50	0/50	2/50	6/50
Hypoalbuminemia (< 3.4 g/dL)	71 (50/70)	26/50	10/50	6/50	0/50	2/50	6/50
Hyperuricemia (> 7 mg/dL)	43 (10/23)	4/10	5/10	0/10	1/10	0/10	0/10

Abbreviations: ADR, adverse drug reaction; CL, cutaneous lymphoma; CRP, C-reactive protein; PRP, pityriasis rubra pilaris; Ps, psoriasis.

findings, but further samples were taken when the clinical course suggested an alternative, more probable, cause. Two patients had been initially diagnosed with eczema, but subsequent biopsies confirmed pityriasis rubra pilaris in one of the cases and psoriasis in the other. Another patient initially diagnosed with psoriasis was ultimately diagnosed with mycosis fungoides plaque after multiple biopsies. Four patients had nonspecific findings in the initial skin biopsies, where the only finding was superficial perivascular dermatitis. The subsequent biopsies confirmed psoriasis in 1 patient and cutaneous lymphoma in the other 3.

The laboratory test results are summarized in Table 3 and show hypoproteinemia and hypoalbuminemia in 49/70 patients (70%), increased C-reactive protein and erythrocyte sedimentation rate in 21/26 (81%), elevated lactate dehydrogenase in 28/35 (80%), hypokalemia in 27/34 (80%), leukocytosis in 25/70 (36%), elevated transaminases in 15/70 (21%), and low hemoglobin counts in 13/70 (19%). Eosinophilia was observed in 46 patients (66%). Twelve patients (26%) had severe eosinophilia in excess of 10%, while 6 (13%) had moderate counts. Seven (20%) of the 34 patients with ADRs and 13 (36%) of the 36 patients with another skin condition had severe eosinophilia. The association was not significant.

Treatment varied according to the underlying cause of the erythroderma. In all cases, drugs considered not strictly necessary or suspected to be implicated were discontinued during hospitalization. Forty-four of the 70 patients were started on corticosteroids after biopsy. Patients with psoriasis identified as a trigger or underlying disease were treated with cyclosporin, acitretin, or infliximab.

Median length of hospital stay was 7 days. Forty-five patients (65%) developed at least 1 complication while in hospital, the most common being skin and soft tissue infection (25/45) (Table 4).

Erythroderma recurred in 9 patients (13%). Median time from resolution of the original episode to relapse was 12 weeks (IQR, 8–22 weeks), and the most common cause was lymphoma (3 patients). Fourteen patients died, 9 of them (65%) within a year of being diagnosed with erythroderma. Just 2 deaths were associated with erythroderma and occurred during hospitalization. One of the patients had

Table 4 In-Hospital Complications.

Complications	No. of patients	ADR	Ps	CL	Eczema	PRP	Other
Skin and soft tissue infection		8/34	8/14	1/9	1/3	1/3	4/7
Heart failure		2/34	0/14	0/9	0/3	0/3	2/7
Acute kidney failure		8/34	0/14	0/9	0/3	0/3	1/7
Catheter-related thrombophlebitis		1/34	3/14	0/9	0/3	0/3	1/7
Need for vasopressor agents		5/34	0/14	1/9	0/3	0/3	1/7
Pneumonia		4/34	1/14	0/9	0/3	0/3	3/7
Septic shock		1/34	1/14	0/9	0/3	0/3	2/7
Deep vein thrombosis		1/34	1/14	2/9	0/3	0/3	0/7

Abbreviations: ADR, adverse drug reaction; CL, cutaneous lymphoma; CRP, C-reactive protein; PRP, pityriasis rubra pilaris; Ps, psoriasis.

Table 5 Mortality in Patients with Erythroderma.

Causes of erythroderma in patients who died	Deaths due to erythroderma, no.	Deaths due to underlying disease responsible for erythroderma, no.	Deaths unrelated to erythroderma or causative disease
Adverse drug reaction	–	2	5
Psoriasis	–	–	1
Mycosis fungoides	–	2	–
Cutaneous T-cell lymphoma	–	1	–
Blistering disease	1	–	–
Graft-vs-host disease	–	–	1
Idiopathic	–	–	1

cutaneous lymphoma and the other developed toxic epidermal necrolysis. Four of the 14 patients with an underlying disorder responsible for the erythroderma died: 1 of fulminant hepatitis secondary to an ADR 1 month after resolution of the erythroderma and 3 due to progression of cutaneous lymphoma (Table 5).

No associations were observed between erythroderma causes and clinical manifestations, laboratory findings, or disease course.

Discussion

Our study has 3 important findings. First, ADRs were main cause of erythroderma, contrasting with other studies in which it was the second most common cause after pre-existing skin conditions.[6–16] Second, vancomycin was the main cause of drug-induced erythroderma. In other studies, carbamazepine, penicillin, and allopurinol were more common.[6,10,11] Third, we did not find any significant associations for any of the study variables or identify any potential predictors of causes, poor outcomes, or mortality.

The rest of the characteristics analyzed were similar to those reported in other series.[6–16] The percentage of patients with acute-onset erythroderma, 76%, is similar to that of 86% reported by Pal et al.[14] The high rate of acute episodes in our series may be linked to the high number of patients with drug-induced erythroderma, as this tends to have an acute onset and generally resolves faster and involves shorter hospital stays than erythroderma with other causes. As mentioned, one of the main findings of our study was that ADRs were responsible for most cases of erythroderma and were most often caused by vancomycin. Drug-induced erythroderma was the second most common form of erythroderma in the series published by Miyashiro and Sanches[16] and Akhyani et al.,[12] and it was largely caused by drugs other than vancomycin. The higher rate of drug-induced erythroderma in our series could be related to the fact that serious ADRs are more common in hospitalized patients. Vancomycin is also widely used in this setting, possibly explaining its predominance in our series (Table 6). Pre-existing skin conditions were the second leading cause of erythroderma at our hospital (30 patients), and in accordance with previous reports,[6–16] a majority of patients had psoriasis or eczema. Like Akhyani et al.[12] and Khaled et al.[6] we observed a low rate of malignancy-related erythroderma. Miyashiro and Sanches[16] and Akhyani et al.[12] reported 17 cases of idiopathic erythroderma. In our series, we were unable to identify the cause in just 1 patient (1.4%), possibly because all patients underwent skin biopsy, and in the event of inconclusive results, biopsies were repeated until a definitive diagnosis was reached.

Fever was associated with ADRs in 5.7% of patients in our series; this is similar to the rate of 6.7% reported by Miyashiro and Sanches.[16] Other clinical manifestations included islands of normal skin (32% of patients in our series vs. 47% in that published by Miyashiro and Sanches), palmoplantar keratoderma (7% vs. 70.3%), edema (25% vs. 62%), and enlarged lymph nodes (24% vs. 65%). The differences might be linked to the predominance of acute drug-induced erythroderma in our series (as this is not generally associated with keratoderma) and the few malignancy-related cases (with minimal lymph node involvement).

Table 6 Characteristics of ADRs implicated in erythroderma.

Types of ADR	Suspected triggers (no. of patients/total patients affected)	Latency of onset, d	Clinical findings, no. of patients/total patients affected	Histopathologic findings	Definitive diagnosis
DRESS (n = 32)	Vancomycin (7/32) Lamotrigine (5/32) Trimethoprim-sulfamethoxazole (4/32) Allopurinol (2/32) Amoxicillin + clavulanic acid (2/32) Piperacillin–tazobactam (1/32) Clindamycin (1/32) Certolizumab (1/32) Ceftriaxone (1/32) Cephalexin (1/32) Bendamustine (1/32) Acyclovir (1/32) Imipenem (1/32) Hydroxychloroquine (1/32) Phenytoin (1/32) Iodinated contrast medium (1/32)	10–30	Morbilliform rash (19/32) Confluent erythema (15/32) Facial edema (5/32) Purpuric lesions (5/32)	Exocytosis of lymphocytes, eosinophilic infiltrate, isolated necrotic keratinocytes	RegiSCAR score ≥4 32/32
TEN (n = 2)	Vancomycin (1/2) Piperacillin–tazobactam (1/2) Phenobarbital (1/2)	7–10	Nikolsky sign (2/2) Asboe-Hansen sign (2/2) Areas of cutaneous detachment (2/2) Confluent erythema (2/2) Mucosal involvement (2/2)	Dermal and epidermal detachment, confluent necrotic keratinocytes, lymphocytic infiltrates	Ingen-Housz-Oro criteria (2/2)

Abbreviations: ADR, adverse drug reaction; DRESS, drug reaction with eosinophilia and systemic symptoms; TEN, toxic epidermal necrolysis.

The laboratory abnormalities observed are similar to those reported by Miyashiro and Sanches in South America.[16] No significant associations were found with other study variables.

It is generally difficult to demonstrate a correlation between histopathologic and clinical findings in erythroderma, as characteristic skin changes seen in given dermatoses overlap with nonspecific inflammatory changes. In our series, the correlation was clearer in patients with drug-induced erythroderma, in whom a definitive diagnosis was reached by evaluating clinical history, triggers, laboratory and histology findings, and diagnostic scores (Table 6). In routine practice, however, it is not always easy to determine the cause of erythroderma based on correlations between histopathologic and clinical findings due to the absence of pre-existing skin conditions, latency periods, distinctive clinical manifestations, and suggestive histopathologic features. Clinical follow-up is essential in the above cases and cases with discordant clinical and pathologic findings. Repeated skin biopsies are advisable in many cases (24 of 70 patients in our series underwent multiple biopsies), and patients with suspected lymphoma should undergo a lymph node biopsy. Median hospital stay was 7 days in our series. None of the other publications consulted reported on length of hospital stay. The mortality rate was 3%, which is similar to rates reported by Rym et al.[7] and Khaled et al.[6] Miyashiro and Sanches[16] and Akhyani et al.[12] described a mortality rate of 1% and 3.8%, respectively. The differences could be due to differences in follow-up time (longer in our series).[6,7,16]

None of the case series analyzed described the treatments used for erythroderma. We are therefore unable to evaluate potential impact on frequency of relapse, remission, or refractoriness. We also found no predictors of specific causes, poor outcomes, or mortality.

Our study has some limitations related to design (retrospective, single-center study with a small sample), selection bias (all the patients were treated in a tertiary referral hospital), and inclusion period (patients were included when the management of erythroderma was changing).

The study, however, also has some strengths. Hospital Italiano de Buenos Aires, for example, is a leading tertiary referral hospital with an integrated, hospital-wide, electronic medical record system in place since 1996. Accordingly, we were able to obtain a complete set of comprehensive, reliable data on the management and follow-up of all patients over a long period.

Erythroderma is difficult to study and challenging to diagnose. Drug-induced erythroderma was the main type of erythroderma identified in our series. Multiple skin biopsies could be key to reaching a definitive diagnosis. Further studies are needed to investigate associations of erythroderma with triggers, laboratory and histopathologic findings, prognosis, and mortality.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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