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Drug Utilization Evaluation of Corticosteroids Based on Safety: A Prospective Observational Study.

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Research Article

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ABSTRACT

In this study we evaluate the utilization of corticosteroids which includes the monitoring of corticosteroid induced adverse effects and analyzing the prescribing habits of corticosteroids. This was a prospective, observational study carried out in 138 patients, for a period of six months. The main clinical adverse effects attributable to corticosteroids were assessed in patients. The relevant datas were collected from patient treatment chart, laboratory investigations, through patient interview and compared with baseline status. The risk factors for steroid induced adverse effects were identified using statistical analysis. BMI of the patients (p=0.019), route of administration (p=0.0001) and dose of steroids (p=0.0001) were showed a positive relationship with the incidence of adverse effects. Prescribing pattern of corticosteroids and the interactions caused by steroids were also analyzed. Out of the total study population 75 were monitored for steroid induced adverse effects.39% showed adverse effects and 61% were free from adverse effects.72.4% experienced single adverse effects, while 27.5% experienced multiple adverse effects. Hyperglycemia was the most frequent adverse effect (62%) observed. Among multiple ADRs hyperglycemia along with hypokalemia was found in more number of patients (6.8%). All patients who received Methylprednisolone experienced adverse effects while Dexamethasone produced adverse effects were found in 90.9%. Among in-patients, most of them were prescribed with Dexamethasone (55%) and in out- patients 41% were treated with Budesonide. Out of total population most of the patients were treated with inhalational steroids (50%) followed by oral (27.11%).Interaction of steroid with co-administered drugs were found mostly in in-patients (83.3%) and only 16.6% was found in out-patients. Till now, effective treatment guidelines for corticosteroids are not available. Even though we can't completely eliminate the occurrence of ADRs, definitely we can minimize it. Further studies are needed for implementing standard Guidelines in corticosteroid therapy.

Keywords: *corticosteroids, adverse effects, prescribing habits, drug utilization evaluation, steroid treatment card, drug interactions.*

Introduction

Drug utilization evaluation (DUE) is a systematic quality improvement activity. This helps to improve the quality and cost effectiveness of drug use and there by helps to improve the patient care. DUE can be applied to a drug, therapeutic class, disease state or a condition, a drug use process or specific outcome. DUE helps in identifying the problems in drug use, reduces adverse drug reactions, optimizing the drug therapy etc[1].

Since 1950s corticosteroids are one of the most commonly prescribed drugs in various diseases due to their anti-inflammatory and immunosuppressive actions. They are widely prescribed in most of the departments. In-spite of their beneficial effects they produces several adverse effects. So evaluations of the corticosteroids are very much important.

The study aims to assess the occurrence of adverse effects and categorize them. Also find out the risk factors which are responsible for adverse effects and analyze the prescribing pattern and drug interactions of steroids.

Methodology

Study design:
It was a prospective observational study.

Study period:
Study was conducted for a period of six months from January 2014 to July 2014.

Study site:
This study was conducted in Kovai Medical Center and Hospital, Tamil Nadu.

Study criteria:

Inclusion criteria

Patients with age above 18 years who were under glucocorticoid therapy.

Exclusion criteria

- Patients on systemic corticosteroid therapy for more than 6 months before the commencement of study.
- Patients with pre-existing diabetes, hypertension, hypothyroidism, Osteoporosis and myopathy, Peptic ulceration, Metabolic and endocrine disorders, Cataract, Glaucoma, Psychiatric problems, IBD.

Sources of data

- Patient case sheet
- Treatment chart
- Laboratory reports
- Patient interview.

Study protocol

Before commencing the study, ethical clearance was obtained from ethical committee of
Kovai Medical Center and Hospital, Coimbatore .Patients who satisfy the inclusion criteria (both in- patients and out-patients) were enrolled in the study which includes cases taken from various departments like Dermatology, Pulmonology, Oncology, General medicine and Neurology. Relevant patient information like patient's demographical details, drug related information's (dose, route, frequency and duration), laboratory investigations and ADRs (if any) etc was collected from case sheet, treatment chart, laboratory reports and through patient interview. Other medications used along with Glucocorticoid therapy were also recorded to check interactions and to ensure that the reported ADRs are due to steroids only. ADRs were assessed in the out patients, inpatients and those in-patients who come for review after discharge.

All the collected data were documented in patient data entry form. Suspected steroid induced ADRs were recorded and assessed by using Naranjo Algorithm for ADR causality assessment, WHO Probability Scale. The severities of ADRs were assessed by ADR Severity assessment Scale (Modified Hartwig and Siegel).

Analyzed the prescribing pattern of Corticosteroids in various departments (Drugs, Dose, Route, and Frequency). Also found out the incidence of interaction of corticosteroids with other drugs.

Result analysis

The causality assessments of suspected ADRs caused by corticosteroids were performed by WHO Probability scale and Naranjo Algorithm. The ADRs were categorized as Probable, Possible and Certain according to the scores given in the Naranjo Algorithm and using WHO Probability scale.
The severities of suspected ADRs were assessed by Modified Hartwig Siegel Scale.

Statistical analysis

Statistical analysis was performed using SPSS Statistical package version 20.0. P value <0.05 is considered as significant. For qualitative variables Chi-square test and comparison of two drugs was done by independent sample T test.

Results & Findings

I) Adverse effects associated with corticosteroids.

Since 1950s Glucocorticoids were one of the most widely used drug for various inflammatory and autoimmune disorders. In spite of their beneficial effects, steroids have several adverse effects, which may sometimes overweigh their beneficial effects and limited their use.
A total of 75 patients were included in this study for ADR assessment. Both inpatients and outpatients prescribed with steroids who visited the hospital during the study period were included and they were followed during their review.

Occurrence of Adverse effects

On assessing the occurrence of ADRs in patients treated with steroids, out of 75 patients, 29 (39%) showed adverse effects, while 46 (61.33%) patients ADRs were absent. Maximum ADRs were found in Dermatology department (38.48%), followed by department of general medicine (31.03%), Pulmonology (17.24%), Oncology (13.79%) and Neurology (3.44%). In Pulmonology department, few patients reported some local adverse effects associated with the use of inhalational steroids.11 patients experienced local adverse effects. Out of this 5 of them had sore throat, 3 had irritating throat, 2 of them had cough during inhalation of corticosteroids. Only one reported oral candidiasis.

Assessment of Risk factors

The demographic datas were analyzed for the risk of development of ADRs. Maximum ADR (42.8%) were shown in the age group of 41-60, followed by 21-40 (40%) and 61-80 (40%) age group. The incidence of ADR in male and female population was analyzed. ADRs were found in 28.94% of male and 48.64% of female. But the age, gender and family history did not show any relation with the incidence of adverse effects.
When we assessed the patients with ADR based on their BMI, 17 were overweight, 8 were normal, 3 were under weight and one obese patient. p value was found to be significant($p=0.019^{*}$). Thus we can say that the BMI of patient is a significant factor in the development of adverse effects in patients treated with steroids.

Individual steroids used in patients and the incidence of adverse effects were analyzed. For that we compared the number of patients with adverse

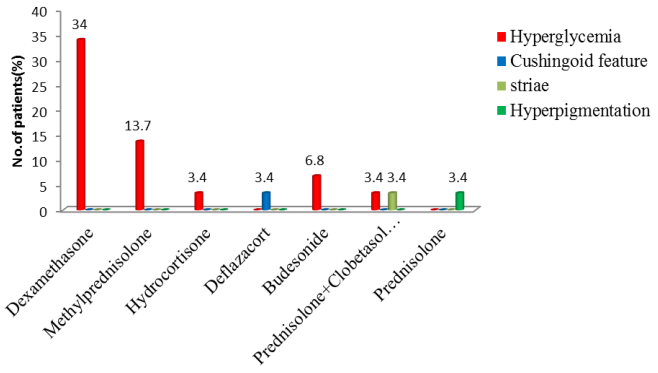
effects and without adverse effects and found that these drugs had significant role in the incidence of adverse effects (p=0.0001*). According to our study Methylprednisolone produces more adverse effects when compared with other steroids.

Table.1: Study population with single adverse effects

Drugs	CATEGORY I			
	Hyperglycemia	Cushingoid features	Striae	Hyperpigmentation
Dexamethasone	10(34)			
Methylprednisolone	4(13.7)			
Hydrocortisone	1(3.4)			
Deflazacort		1(3.4)		
Budesonide	2(6.8)			
Prednisolone+Clobetasol propionate	1(3.4)		1(3.4)	
Prednisolone				1(3.4)

In this Prospective analysis, the relation between the incidence of AEs and the route of administration of steroids were assessed. Intravenous administration produces more adverse effects .The p value found to be significant (p=0001*).Thus we can say that the route of administration of steroids is a significant risk factor for the development of adverse effects.

Figure1: Study poulation with single adverse effects



Comparison of Dexamethasone and Methylprednisolone

As methylprednisolone and dexamethasone produces more adverse effects among all corticosteroids, we compared both these drugs and found that the dose have significant influence (p=0.0001*). Methylprednisolone given higher dose more and it produces more adverse effects when compared with Dexamethasone .While age and BMI of patients have no influence on the ADRs produced by these two drugs.

Incidence of adverse effects in individual patients

In our study we analyzed the occurrence of adverse effects in individual patients. For this purpose we categorized the study population in to patients with single ADRs and patients with multiple ADRs (Category I& Category II).Among 29 patients, 21 patients had single ADRs and 8 experienced multiple ADRs.31% had hyperglycemia due to Dexamethasone, while 13.7% developed due to Methylprednisolone ,6.8% by Budesonide and 3.4% due to Methylprednisolone + Clobetasol combination. Cushingoid features found in 3.4% by Deflazacort. Prednisolone developed hyperpigmentation in 3.4% and 3.4% experienced striae due to Methylprednisolone+ Clobetasol combination [Table.1, Figure.1].

Prednisolone induced hyperglycemia and weight gain was found in one patient. Hydrocortisone induced hypokalemia+ hyperglycemias were found in 2 patients and hyperglycemia and striae were reported in one patient. One patient experienced both hyperglycemia and cushingoid features due to Methylprednisolone. Hyperglycemia and gastric irritation were found in one patient with Prednisolone + Clobetasol combination. Deflazacort developed weight gain and gastric irritation in one patient and cushingoid features and gastric irritation in another patient [Table.2, Figure.2].

Onset of adverse effects and their management

In most of the in-patients, adverse effects (hyperglycemia and hypokalemia) were developed following the first day of administration of steroids. Among 24 hyperglycemic patients, 19 were not given any treatment, 3 were treated with insulin, one with oral hypoglycemic agent and one with the combination of oral hypoglycemic agent and insulin. Among hyperglycemic patients, 2 became normalized by the reduction of dose and one by the stoppage of steroids. Steroid induced hypokalemia was treated with Potassium chloride syrup. In case of out - patients, the onset of adverse effects is difficult to measure as it can be assessed only at the time of review. Among out-patients, gastric irritation was treated by increasing the dosing frequency of proton pump inhibitors and H_2 blockers (od to bd).Cushingoid features due to higher dose of corticosteroids, reported after 30 days got normalized by reduction of dose.

Categorization of adverse effects

Adverse effects of corticosteroids were categorized using Naranjo Causality assessment Scale and WHO probability Scale. According to Naranjo Causality assessment Scale, out of 29 patients, 17 were Probable and 12 were Possible. 19 were Probable, 8 were Possible and 2 of them were in Certain category based on WHO probability Scale.

When we assessed the severity of adverse effects, 12 patients have Mild adverse effects (level 2).17

patients had Moderate ADRs, out of this 15 were under level 3 and 2 under level 4(a).

Table 2 :Study Population with multiple adverse effects.

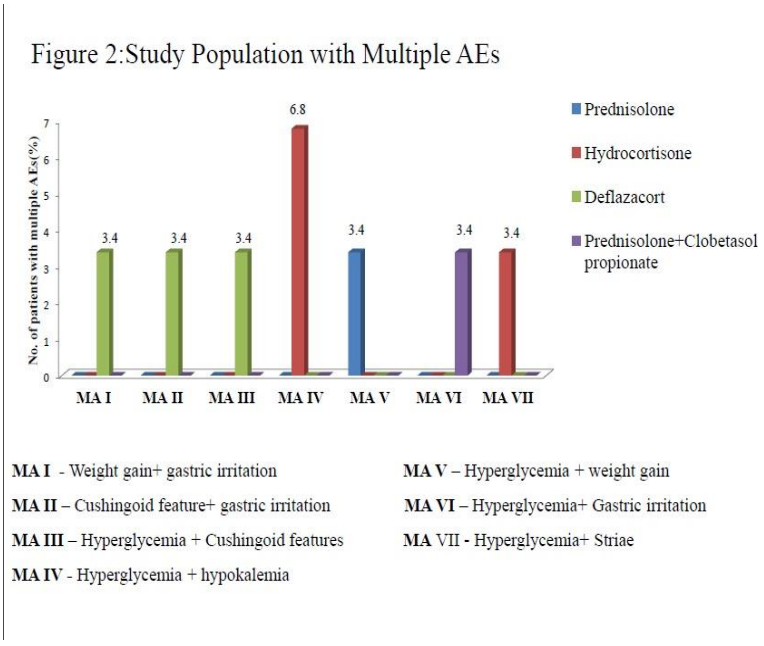
Table 12: Study Population with Multiple AEs

DRUGS	CATEGORY II						
	Weight gain + Gastric irritation	Cushingoid features + Gastric irritation	Hyperglycemia + Cushingoid features	Hyperglycemia + Hypokalemia	Hyperglycemia + Weight gain	Hyperglycemia + Gastric irritation	Hyperglycemia + Striae
Prednisolone					1(3.4)		
Hydrocortisone				2(6.8)			1(3.4)
Deflazacort	1(3.4)	1(3.4)	1(3.4)				
Prednisolone + Clobetasol propionate						1(3.4)	

II) Prescribing pattern of corticosteroids

Corticosteroids are one of the most commonly prescribed drugs in various diseases due to their anti-inflammatory and immunosuppressive action. They are widely prescribed in most of the departments, but there are no specific standard prescribing guide-lines for them, only individual guidelines for diseases are available. The irrational prescribing of corticosteroid produces severe adverse effects, so standard guidelines of corticosteroids should be developed.

Figure 2: Study population with multiple adverse effects



i – Prescribing pattern of corticosteroids in Pulmonology.

A total of 62 patients (59 outpatients and 3 inpatients) were treated with corticosteroids. Out of this 46% were male and 53.9% were female. The mean age of these patients was 49.61 ± 17.22. The maximum use of steroids was observed in 41 - 60 age group (39.6%). Most of the patients were treated for asthma (68.25%), COPD (12.6%), Allergic rhinitis, (12.6%). 1.5% of ILD, bronchiectasis, pulmonary TB. While considering the steroid usage, Budesonide + formoterol combination (Budamate 400 mcg) was prescribed in most of the patients (52.3%) followed by 200 mcg (20.63%). 91.93% were treated with monotherapy and remaining 8.06% with combination therapy. Based on route of administration inhalation was given in 92% of patients while intravenous and nebulization for 3.2% and oral therapy for 3.1% .

ii – Prescribing pattern of corticosteroids in Dermatology.

In dermatology, 58 patients (53out patients+5 inpatients) were treated with corticosteroids. Among this study population 65.5% were found to be male and 34.48% female. The mean age of study population was found to be 42.15±15.33.Majority of the patients were comes under the age group of 41-60 (41.37%).

Most of the patients administering corticosteroid were treated for Eczema (24.13%) followed by LP (13.7%),Vitiligo(12.6%),Utricaria(6.8%),LSC& Psoriasis(5.16%), and 3.4% of PUPP, Alopecia aerate, Pemphigus vulgaris, Ulcers, Bulluspemphigoid and 1.7% of SLE, Paniculitis, Pompholyx, Actenereticuloid etc.

Based on steroid prescribed, most of the patients were treated with Prednisolone and Clobetasol propionate combination (27.58%) followed by Betamethasone 0.5mg (17.2%), Prednisolone 10mg (12%) and Prednisolone 20mg (10.3%).While considering route of administration, oral steroids were given for most of the patients (44.8%),

followed by combination of oral and topical (27.58%), topical (17.27%) and iv (8.6% was given in in-patients).

iii – Prescribing pattern of corticosteroids in Department of General medicine.

12 patients (6 out patients & 6 inpatients) were administered with steroids, out of which 12.5% were male and 83.35% were female. Mean age of study population was found to be 45.58±15.77. Majority of patients were under the age group of 41-60 (50%).Out of the study population most of them were treated for Rheumatoid arthritis (41.6%) followed by Immune thrombocytopenia (16.66%), Allergic rhinitis (16.66%), Allergy (8.3%) and Fever (8.3%).

Maximum of patients were treated with Deflazacort (newer steroid) especially in out patients (33%). 25% were administered with Hydrocortisone, 8.3% with Dexamethasone, MP and Fluticasone. Based on route of administration 33.3% were treated with oral corticosteroids (all are out patients), 16.16% were treated by inhalational and remaining 33.3% were by intravenous corticosteroids (in-patients).

iv – Prescribing pattern of corticosteroids in Oncology and Neurology.

In Oncology department 5 patients and in Neurology one patient was treated with Dexamethasone. In Oncology mean age of study population was found to be 55.± 16.32 .The data shows that the maximum use of corticosteroids were observed in the age group of 61-80. Gender distribution showed that 2 were male and remaining female.

The use of steroids in various diseases showed that, in cancer (83.33%) and in Tolosa hunt syndrome (16.66%). All patients were treated with Dexamethasone and administrated intravenously [Table.17&Table.19]. A total of 12 corticosteroids were prescribed in five departments of the hospital.

Among 3 major categories of steroids in in-patients, most widely used steroid was Dexamethasone (55%),followed by Methylprednisolone(25%) and Hydrocortisone(20%) and based on the route , 95% were administered intravenously and 5% with oral steroids.

In out-patients, 41.52% were treated with Budesonide and formoterol combination in pulmonology department.13.5% with Methylprednisolone and clobetasol combination, 11% with Methylprednisolone, 8.4% with Clobetasol, 8.4% Betamethasone, 7.62% Fluticasone,5% with Deflazacort and 5% by other steroids.

While considering the route of administration, maximum number of patients were treated with inhalational steroids (50%) followed by oral (27.11%), combination of oral and topical (13.55%), and topical steroids (10.1%) among out-patients. The selections of dose of steroids were based on the empirical datas of patients.

Incidence of drug interactions

We monitored each prescription for the assessment of interaction of corticosteroids with other drugs prescribed along with them. We found 18 drug-drug interactions. Out of this 15 were moderate, 2 were minor and one interaction was major. The incidence of interaction was statistically significant (p=0.0001*) and more associated with in-patients. So in order to prevent more interactions, careful prescribing should be there.

Discussion

Assessment of adverse effects of corticosteroids

In our study we found that 39% of patients had experienced at least one adverse effect within the study period. L.Fardet *et al.*, carried out a study regarding the clinical adverse effects of corticosteroid and found that 71% of patients experienced at least one adverse effect during the first 3 months of therapy.

On assessing the risk factors of steroid induced adverse effects, this study showed that, there is no relationship between the age of the patient and steroid induced adverse effects. Gonzalez-Gonzalez *et al.*, also could not find any relationship between the age and steroid induced AEs. In contrast, L.Fardet *et al.*, found out a positive relationship between the age and incidence of lipodystrophy and muscle cramps.

In our case series, adverse effects were found in 37.93% of male and 62.06% of female and the gender was found to have no relationship with the development of AEs. Same happened in the study conducted by Gonzalez-Gonzalez *et al.*,. But according to L.Fardet *et al.*,, gender was a risk factor for the development of Lipodystrophy and cutaneous adverse effects.

We compared BMI of patients with ADR and without ADR, and concluded that it was a significant risk factor ($p=0.019^{*}$) in the development of ADRs. But Gonzalez-Gonzalez *et al.*,, in their study did not found any relation. In concordance with the study done by Gonzalez *et al.*, family history did not have any influence in our study as well.

We analyzed the individual steroid use in patients and the incidence of adverse effects and found that the drug had a significant role in the incidence of adverse effects.

According to the study, route of administration of steroids had influence in the development of adverse effects and it showed a significant p value. Similar to our study Blackburn D *et al.*,, found out a relationship between the oral and inhalational steroids and incidence of hyperglycemia. In their study oral steroids produces more hyperglycemia than the inhalational steroids. Whereas in our study intravenous steroids produces more AEs followed by oral, oral and topical combination.

On comparing the cumulative dose of steroids, with the incidence of adverse effects it was statistically significant. In the study of corticosteroids and

adverse events by L.Fardet *et al.*, also found a significant relationship between cumulative dosage and lipodystrophy.

In our study, among the adverse effect detected 62% had hyperglycemia and three had cushingoid features along with other adverse effects. While in a similar study done by L.Fardet *et al.*, 63% experienced lipodystrophy and 53% experienced insomnia. In another study carried out by Mc Donough *et al.*, the most self- reported adverse effect was weight gain followed by skin bruising or thinning and sleep problem. But in our study weight gain found in only 6.8% of patients along with other adverse effects. 3 patients experienced gastric irritation along with other adverse effects in this study. A prior study done by Hernandez-Diaz. S *et al.*, concluded that the risk of upper gastrointestinal complication was 1.8 times higher for oral steroid users than non-users and the risk was greater for higher dose of steroids than the lower dose.

In this study, inhalational steroids developed hyperglycemia was found in 2 patients. This was developed as a result of higher dose of Budesonide. Previous study done by Suissa *et al.*, also found that the use of corticosteroid is associated with a significant 34% increase in the risk of incidence of diabetes and the risk increased with higher dose of inhalational steroids (1000µg of fluticasone/day or equivalent).

The local adverse effects due to inhalational steroids were found in 11 patients in our study. Among these most of them experienced Sore throat (45.45%), followed by irritating throat (27.27%),cough during inhalational steroids (18.18%) and oral candidiasis (9.09%),i.e. Pharyngeal symptoms were found in all patients. Similar symptoms were found by CR. Pinto *et al.*, in his study along with other local adverse effects.

Prescribing pattern of corticosteroids

According to this study, maximum numbers of patients (46.3%) were treated for respiratory diseases followed by dermatological conditions (40.02%). Similar study was carried out by Ramanath *et al.*, and found that most of the patients were treated for respiratory diseases. And also most of the patients were treated with Budesonide in pulmonology department in this study and this was supported by the study carried out by Rajalingam *et al.*,.

In a study conducted by Ramanath *et al.*,, among IP patients the most widely used steroids was Budesonide (60.6%) and Dexamethasone was prescribed least. But opposite to that in our study the most prescribed steroid was dexamethasone.

Based on the route of administration of steroids, 95% administered intravenously and 5% took oral and topical steroids .But Ramanath *et al.*, concluded that Nebulization was the most frequently used route of administration among IP patients.

A study conducted by Ramanath *et al.*, showed that the incidence of drug interaction due to steroids were observed mostly in in-patients and was statistically significant. A similar result was obtained in this study also.

Conclusion

Corticosteroids are widely prescribed in modern medicine, forming a part of standard treatment for a wide range of disorders which feature inflammation and/or immune activation. Apart from their beneficial effects they produce number of adverse effects.

In this study, we monitored the corticosteroid induced adverse effects and most of the patients experienced Hyperglycemia. Other adverse effects like Cushingoid appearance, Hypokalemia, Gastric irritation, Weight gain, Cutaneous adverse effects like Striae and Hyperpigmentation were also reported. Some of the patients showed only one AEs while others showed more than one (due to higher dose of corticosteroids).

BMI of the patient, cumulative dose and the route of administration of drugs were significant risk factor for the development of adverse effects. While age, gender, family history of patients did not have any influence in the development of steroid induced adverse effects.

Methylprednisolone produces adverse effects in all patients (100%) while Dexamethasone in 90.9% when compared with other steroids.

The comparison of the dose of Methylprednisolone and Dexamethasone showed that cumulative dose of steroid is a risk factor for the development of adverse effects.

Analysis of prescription showed that the occurrence of drug interactions were more in in-patients and was statistically significant.

Till now, effective treatment guidelines for corticosteroids are not available. Even though we can't completely eliminate the occurrence of ADRs, definitely we can minimize it. Further studies are needed for implementing standard Guidelines in corticosteroid therapy and all hospitals should implement steroid treatment card to improve the quality of life of the patients.

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AUTHORS' CONTRIBUTIONS

Authors contributed equally to all aspects of the study.

PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.