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RESEARCH

# Undiagnosed adrenal insufficiency as a cause of premature death in glucocorticoid users

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## Abstract

*Objective:* It is unknown whether glucocorticoid (GC)-induced adrenal insufficiency may cause premature mortality in GC users. We conducted a retrospective cohort study to investigate if undiagnosed and undertreated GC-induced adrenal insufficiency is a contributor to premature death in GC users.

*Methods:* Information on dispensed prescriptions in West Sweden from 2007 to 2014 was obtained from the Swedish Prescribed Drug Register. Cause of death was collected from the Swedish Cause of Death Register. Of 223,211 patients who received oral GC prescriptions, 665 died from sepsis within 6 months of their last prescription. Three hundred of these patients who had died in hospital were randomly selected for further investigation. Medical records were initially reviewed by one investigator. Furthermore, two additional investigators reviewed the medical records of patients whose deaths were suspected to be caused by GC-induced adrenal insufficiency.

*Results:* Of 300 patients (121 females, 40%), 212 (75%) were prescribed GC treatment at admission. The mean age was 76 ± 11 years (range 30–99). Undiagnosed or undertreated GC-induced adrenal insufficiency was considered a probable contributor to death by at least two investigators in 11 (3.7%) patients. In five of these 11 cases, long-term GC therapy was abruptly discontinued during hospitalization. Undiagnosed or undertreated GC-induced adrenal insufficiency was considered a possible contributing factor to death in a further 36 (12%) patients.

*Conclusion:* GC-induced adrenal insufficiency is an important contributor to premature death in GC users. Awareness of the disorder during intercurrent illness and following cessation of GC treatment is essential.

Keywords: oral glucocorticoids; mortality; adrenal insufficiency; sepsis

## Introduction

Oral glucocorticoid (GC) treatment can lead to adrenal insufficiency by suppressing the hypothalamic–pituitary–adrenal axis. This can result in life-threatening adrenal crisis if the patient does not receive an increased GC dose (stress dose) during physical and/or psychological stress. Similarly, patients undergoing severe stress who have recently ceased GC treatment also require stress doses of GC (1). Common symptoms and signs of adrenal crisis include hypotension, abdominal pain, nausea, vomiting, fever, and fatigue,

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which can be misdiagnosed as an infection or sepsis (1, 2). Adrenal crisis-associated mortality is 6% (1). The incidence of adrenal crisis in patients with primary and secondary adrenal insufficiency is 3.6–8.3 per 100 patient-years (1, 3), but in patients with GC-induced adrenal insufficiency, the incidence is 15.1 per 100 patient-years (3).

Fatal cases of GC-induced adrenal insufficiency have been reported (4, 5), the incidence of which remains unknown. A previous study reported increased mortality in long-term GC users in the first 2 months following cessation of GC treatment (6). This raises concerns about undiagnosed and undertreated adrenal crisis being a clinical problem in this group of patients (7). The aim of this study was to assess if adrenal insufficiency is associated with the cause of death in oral GC users.

## Methods

This was a retrospective study based on a cohort from our previous epidemiological studies on GC users between 2007 and 2014 in Västra Götaland County, Sweden (8, 9). Data were collected from the Swedish Prescribed Drug Register using the Anatomical Therapeutic Chemical codes for oral GCs (prednisolone H02AB06; hydrocortisone H02AB09; betamethasone H02AB01; and dexamethasone H02AB02). Of the 1,585,335 inhabitants of Västra Götaland County, 223,211 patients received a GC prescription at doses associated with a risk of developing GC-induced adrenal insufficiency, i.e. prednisolone (or the equivalent dose of other GC) at a dose of ≥5 mg daily for ≥21 days (8). Using their personal identification number, these patients were cross-linked with the Swedish Cause of Death Register, where information on the date of death; the primary cause of death; and contributing causes of death were collected. ICD-10 codes *A40 Streptococcal sepsis* and *A41 Other sepsis* were used to find all patients who died of sepsis.

Of the 223,211 patients with chronic GC use, 665 died of sepsis within 6 months of their last dispensed oral GC prescription. Data from a random sample of 300 of these patients who died of sepsis, all of whom died in hospital, were collected for further investigation. The random sample was created by using a random number generator in Microsoft Excel 2016.

### Review of medical records

A total of 300 randomly selected medical records were reviewed to determine if the death was unrelated to, possibly related to, or probably related to GC-induced adrenal insufficiency. Past medical history, duration of, and indication for, GC use, symptoms and signs before death, and biochemical data were collected. One investigator conducted the initial review and estimated if it was unlikely, possible, or probable that the death had been related to GC-induced adrenal insufficiency. Following this initial review, 51 deaths were considered possibly or probably related to GC-induced adrenal insufficiency. Death probably caused by GC-induced adrenal insufficiency was defined as death in which GC-induced adrenal insufficiency was a major contributing factor to the cause of death (e.g. if GC stress dose had been given, the patient would most likely have survived). Death possibly related to GC-induced adrenal insufficiency is defined as death in which GC-induced adrenal insufficiency was a contributing factor but not a dominant factor (e.g. if GC stress dose had been given, the patient may have survived or died). Each of these 51 medical records was subsequently independently reviewed by two additional investigators in the following manner: one investigator reviewed all 51 cases, and two additional investigators reviewed 26 and 25 of these cases each. Thus, all 51 medical records were reviewed by three investigators. All investigators are experienced endocrinologists. During the review process, the investigators were unaware of each other's grading. Two reviewers had to agree for a death to be considered as unlikely, possibly, or probably related to GC-induced adrenal insufficiency. However, in three cases, all reviewers disagreed (one said unlikely, one possible, and one probable). In these three cases, the death was classified as possibly related to GC-induced adrenal insufficiency. Since plasma cortisol was not measured before death, the grading 'possibly or probably related to GC-induced adrenal insufficiency', was not considered to confirm the diagnosis; it rather depicts the authors' assumption based on information gathered from the medical records.

### Ethics statement

The study was approved by the Regional Research Ethics Committee in Gothenburg, Sweden (reference number 773-14; approved March 9, 2015) and by the National Board of Health and Welfare, Sweden.

### Statistical analysis

Age was defined as the age at death. Only patients with ongoing GC treatment on admission were included in the calculations of treatment duration and GC dosage. The prednisolone-equivalent dose was calculated as follows: prednisolone 5 mg = hydrocortisone 20 mg = dexamethasone 0.5 mg = betamethasone 0.5 mg.

Descriptive data are presented as mean ± S.D. and/or median (range). For the comparison of groups, Student's *t*-test was used for continuous variables with a normal distribution, and the Mann–Whitney *U* test for non-normally distributed continuous variables.

Fisher's exact test was used to estimate the differences between categorical variables. All analyses were conducted using IBM SPSS Statistics for Windows, version 25 (IBM Corp). A *P*-value < 0.05 was considered statistically significant.

## Results

Of the 300 patients studied (121 women, 40.3%), 209 (69.7%) had ongoing GC treatment at hospital admission (Table 1). The mean age was 76 ± 11.5 years (range 30–99). The median GC dose (prednisolone-equivalent dose) was 15 (range 1.25–160), and the median treatment duration was 6 (range 0.1–78) months. Of the 300 patients, 51 were selected for further evaluation by the first investigator. At least two reviewers agreed in 94% of the cases. Of these 51 patients, 47 deaths were considered to be related to GC-induced adrenal insufficiency (Table 1). These 47 patients had lower GC doses prior to admission ($P = 0.002$), lower systolic blood pressure on admission ($P = 0.018$), and a higher likelihood of gastrointestinal symptoms ($P = 0.003$) and hypoglycemia ($P < 0.001$) compared to the group whose death was not considered to be related to their GC treatment ($n = 253$). The plasma-sodium levels did

**Table 1** Comparison of the two subgroups ($n = 253$ and $n = 47$) following the review of medical records.

| | **All patients** ($n = 300$) | **Review indicates that the patient died from sepsis** ($n = 253$) | **Review indicates that GC-induced AI contributed to death** ($n = 47$) | ***P*** |
|---|---|---|---|---|
| Age (years) | | | | |
| Mean (S.D.) | 76 (11.5) | 76 (11.7) | 76 (10.1) | 0.903 |
| Median (range) | 77 (30–99) | 77 (30–99) | 76 (48–93) | |
| Gender | | | | |
| Men | 179 (60%) | 149 (59%) | 30 (64%) | 0.526 |
| Women | 121 (40%) | 104 (41%) | 17 (36%) | |
| Ongoing GC on admission | 212 (75%)[a] | 178 (73%)[a] | 33 (70%) | 0.575 |
| GC treatment >3 months | 128 (45%)[b] | 105 (45%)[b] | 23 (49%) | 0.417 |
| GC dose (PED) | | | | |
| Mean (S.D.) | 23.8 (26.1)[c] | 25.8 (27.6)[c] | 13.6 (11.5) | |
| Median (range) | 15.0 (1.25–160)[c] | 15.0 (1.25–160)[c] | 10 (2.5–40) | 0.002 |
| Length of GC treatment (months) | | | | |
| Mean (S.D.) | 13.9 (17.9)[b] | 13.0 (16.9)[b] | 17.6 (17.2) | |
| Median (range) | 6.0 (0.1–78)[b] | 5.5 (0.1–78)[b] | 14.1 (0.5–71) | 0.106 |
| Systolic blood pressure (mm Hg) on admission | | | | |
| Mean (S.D.) | 116 (28.9)[d] | 118 (28.8)[d] | 107 (27.6)[d] | 0.018 |
| Median (range) | 113 (59–210)[d] | 115 (59–210)[d] | 102 (65–170)[d] | |
| Fluid-resistant hypotension | 106 (36%)[e] | 73 (30%)[e] | 33 (70%) | <0.001 |
| Gastrointestinal symptoms | 51 (17%) | 36 (14%) | 15 (32%) | 0.003 |
| Hypoglycemia | 13 (6.3%)[f] | 6 (3.5%)[f] | 7 (20%)[f] | <0.001 |
| Plasma sodium (mmol/L) | | | | |
| Mean (S.D.) | 136.3 (6.5)[g] | 136.2 (6.1)[g] | 137.1 (8.1)[g] | 0.408 |
| Median (range) | 136 (118–179)[g] | 136 (118–159)[g] | 136 (122–179)[g] | |
| ICU admission | 72 (24%) | 54 (21%) | 18 (38%) | 0.038 |
| Increased GC dose during hospitalization | 119 (40%)[h] | 110 (44%)[h] | 9 (19%) | 0.002 |
| Autopsy performed | 16 (5.3%) | 12 (4.7%) | 4 (8.5%) | 0.381 |

[a]Information is missing for nine patients in the group where sepsis is considered to be the cause of death.
[b]Information is missing for 18 patients in the group where sepsis is considered to be the cause of death.
[c]Information is missing for 13 patients in the group where sepsis is considered to be the cause of death.
[d]Information is missing for 15 patients (14 patients in the group where sepsis is considered to be the cause of death and 1 patient in the group where GI-A is the suspected to be the cause of death).
[e]Information is missing for seven patients in the group where sepsis is considered to be the cause of death.
[f]Information is missing for 92 patients (78 patients in the group where sepsis is considered to be the cause of death and 14 patients in the group where GI-A is the suspected cause of death).
[g]Information is missing for 46 patients (40 patients in the group where sepsis is considered to be the cause of death and 6 patients in the group where GI-A is the suspected cause of death).
[h]Information is missing for 5 patients; all were in the group where sepsis is considered to be the cause of death.
AI, adrenal insufficiency; GC, glucocorticoids; ICU, intensive care unit; PED, prednisolone-equivalent dose.

not differ between the groups. The indications for GC therapy and comorbidities were not statistically different between these two groups (Table 2).

## Deaths where GC-induced adrenal insufficiency was probably involved

We identified 11 (3.7%) cases where undiagnosed and untreated GC-induced adrenal insufficiency probably contributed to the patient's death (Fig. 1). In 5 of these 11 cases, long-term (>30 days) GC treatment was discontinued for unknown reasons during the hospital stay. One patient received an increased GC dose for unknown reasons several hours before death. The following four cases illustrate patients from this group.

### Case 1

An elderly patient was admitted due to abdominal pain, loss of appetite, and fever (39°C). Four days prior to admission, the patient discontinued a 15-day course of prednisolone (30 mg for 5 days, 20 mg for 5 days, and 10 mg for 5 days). The prednisolone was prescribed for chronic obstructive pulmonary disease. During the hospital stay, cholecystitis was suspected, although an ultrasound of the liver was normal. The patient received treatment with antibiotics and intravenous (IV) fluids. Despite this, the patient´s condition worsened, and he was admitted to the ICU due to treatment-resistant hypotension and somnolence. During the next 2 days, the patient developed multi-organ failure and died without receiving any GCs.

### Case 2

An elderly patient with polymyalgia rheumatica, who had been taking prednisolone for 9 months (3.75 mg/day), was admitted with acute gout. The prednisolone dose was increased upon admission to 10 mg/day, and the patient soon felt much better. Following the transfer from one inpatient ward to another, the prednisolone treatment was discontinued. A few days later, the patient complained of dizziness, especially when in an

**Table 2** Comparision of the indication for glucocorticoid treatment and comorbidity between groups after review of medical records.

| | **All patients** (*n* = 300) | **Review indicates that the patient died from sepsis** (*n* = 253) | **Review indicates that GC-induced AI contributed to death** (*n* = 47) | ***P*** |
|---|---|---|---|---|
| **Indication for GC treatment** | | | | |
| Malignant neoplasm | 94 (31%) | 77 (30%) | 17 (36%) | 0.494 |
| Hematological malignancy | 52 (17%) | 48 (19%) | 4 (8.5%) | 0.095 |
| PMR | 26 (8.7%) | 21 (8.3%) | 5 (11%) | 0.576 |
| COPD and asthma | 25 (8.3%) | 20 (7.9%) | 5 (11%) | 0.564 |
| Rheumatological conditions[a] | 22 (7.3%) | 17 (6.7%) | 5 (11%) | 0.360 |
| Skin disorders | 10 (3.3%) | 8 (3.2%) | 2 (4.3%) | 0.659 |
| Nonspecific inflammation, high ESR | 10 (3.3%) | 7 (2.8%) | 3 (6.4%) | 0.195 |
| Other pulmonary diseases | 7 (2.3%) | 7 (2.8%) | 0 | 0.601 |
| IBD | 3 (1.0%) | 3 (1.2%) | 0 | 1.000 |
| Allergy | 3 (1.0%) | 3 (1.2%) | 0 | 1.000 |
| Adrenal insufficiency | 3 (1.0%) | 2 (0.8%) | 1 (2.1%) | 0.401 |
| ITP | 3 (1.0%) | 2 (0.8%) | 1 (2.1%) | 0.401 |
| Post-transplantation | 2 (0.7%) | 2 (0.8%) | 0 | 1.000 |
| Inflammatory liver disease | 1 (0.3%) | 1 (0.4%) | 0 | 0.289 |
| Unknown | 39 (13%) | 35 (14%) | 4 (8.5%) | 0.478 |
| **Comorbidities** | | | | |
| Malignancy | 181 (60%) | 153 (60%) | 28 (60%) | 1.000 |
| Hypertension | 77 (26%) | 65 (26%) | 12 (26%) | 1.000 |
| Diabetes | 63 (21%) | 50 (20%) | 13 (28%) | 0.243 |
| Heart failure | 58 (19%) | 46 (18%) | 12 (26%) | 0.234 |
| Ischemic heart disease | 56 (19%) | 45 (18%) | 11 (23%) | 0.414 |
| Stroke | 33 (13%) | 28 (11%) | 5 (11%) | 1.000 |
| Thromboembolism | 6 (2%) | 6 (2.4%) | 0 (0%) | 0.595 |

[a]Inflammatory polyarthropathies (ICD-10 codes M05-M14) and systemic connective tissue disorders (ICD-10 codes M30-M36 (not M35.3, M31.5 or M31.6)).
AI, adrenal insufficiency; COPD, chronic obstructive pulmonary disease; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; ITP, idiopathic thrombocytopenic purpura; PMR, polymyalgia rheumatica.

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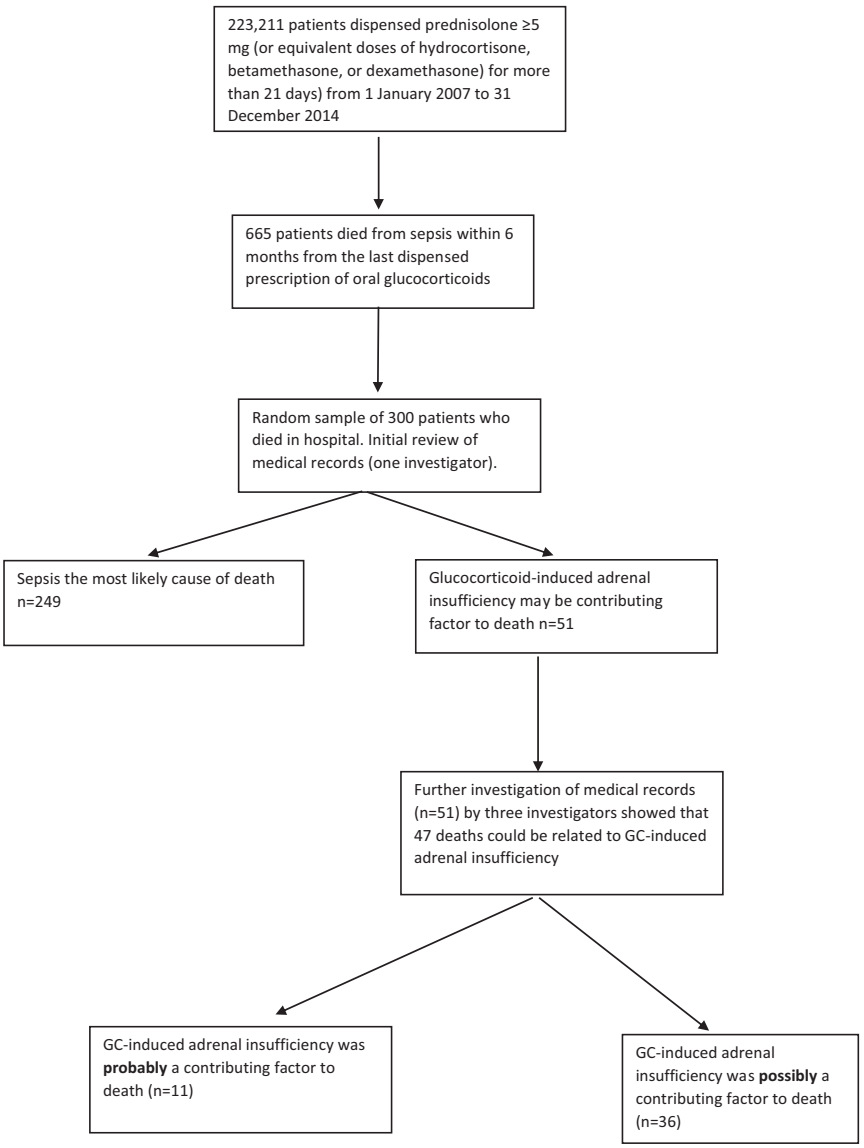


**Figure 1**

Flowchart showing the study design.

upright position. Systolic blood pressure was 60 mm Hg and remained low (80 mm Hg) despite 3 L of IV fluids. C-reactive protein (CRP) was greatly elevated, and the patient commenced antibiotic treatment. The patient died 2 weeks later, presumably due to sepsis. Neither prednisolone nor any other GC was administered.

### Case 3

An elderly patient with confirmed GC-induced adrenal insufficiency presented with abdominal pain, hematuria, and an elevated CRP. The patient had been taking hydrocortisone 30 mg per day for 5 months. On arrival, the systolic blood pressure was 120 mm Hg. Two hours later, the systolic pressure had dropped to 80 mm Hg, and he was therefore transferred to the ICU. He died 19 h after hospital arrival, without having received any stress dose of GC.

### Case 4

An elderly patient with polymyalgia rheumatica, taking 15 mg of prednisolone daily and had been on GC treatment for 10 months, presented with gastrointestinal bleeding. On admission, systolic blood pressure was 80 mm Hg and hemoglobin was 97 g/L. The patient was kept fast, and all oral medications were temporarily discontinued. IV fluids, blood transfusions, and antibiotics were administered. No GCs were given during the hospital stay. After gradual deterioration, the patient was unexpectedly found dead in his bed 3 days later.

## Deaths where GC-induced adrenal insufficiency was possibly involved

Undiagnosed or undertreated GC-induced adrenal insufficiency was considered to be a possible contributing factor of death in 36 patients (12%). In 7 of

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these 36 cases, long-term (>30 days) GC treatment was discontinued for unknown reasons during the hospital stay. Eight patients received an increased GC dose during hospitalization. The dosage of GC was increased in three patients due to suspected GC-induced adrenal insufficiency, in two patients due to allergy, in one patient due to nausea, and in one patient for unknown reasons. The following two cases illustrate patients from this group.

### Case 5

An elderly patient with lethargy, weight loss, and a high erythrocyte sedimentation rate was started on prednisolone 20 mg daily. The patient was diagnosed with cancer 2 months later, and tapering of the prednisolone was initiated. Two weeks after the initiation of tapering, the patient underwent an operation for the cancer. Preoperatively, the patient received 50 mg of IV hydrocortisone. After the operation, he developed pneumonia and atrial fibrillation. He was hypotensive and hyponatremic (128–136 mmol/L). No GC stress dose was administered. The patient received prednisolone 2.5 mg daily until he died 1 month after the operation.

### Case 6

A patient in her 70s received a prescription for prednisolone and was recommended to take 30 mg daily before slowly tapering. The indication for the treatment is unknown. Two weeks later she was admitted with a wound infection. Blood cultures showed the growth of *Staphylococcus aureus*. She had a systolic blood pressure of 90 mm Hg and was tachycardic. On admission, the prednisolone treatment was discontinued for unknown reasons. Her condition deteriorated slowly after admission, and she died 9 days later.

In these last two cases, where GC-induced adrenal insufficiency was considered to be a possible contributing factor, one patient received a single stress dose (case 5), and the other had a relatively short GC treatment duration (case 6). So GC-induced adrenal insufficiency possibly contributed, although adequate GC treatment may not have saved their lives.

Taken together, based on the factors contributing to the adrenal crisis, these cases can be divided into two groups: (A) adrenal crisis following GC cessation, and (B) adrenal crisis due to lack of stress dose administration. Thus, group A includes cases 1, 2, 4, and 6, and group B includes cases 3 and 5.

## Discussion

This retrospective cohort study, including 300 randomly selected GC users who died from sepsis, shows that a significant number of patients (15.7%) had an undiagnosed or undertreated GC-induced adrenal insufficiency that either possibly or probably contributed to their death. This is the first study to investigate if undiagnosed GC-induced adrenal insufficiency is causing premature mortality. In this study, we identified two main groups: cases with adrenal crisis following GC cessation, and cases where stress doses should have been administered.

### Adrenal crisis following GC cessation

The period after GC treatment cessation is potentially life-threatening if the hypothalamic–pituitary–adrenal axis has not recovered (5). Up to 90% of patients have suppressed adrenal function for several days after short-term oral GC treatment (10, 11), and the recovery can take from several days to several months (10, 11). As an example, in case 1, the patient contracted an infection 4 days after cessation of GCs, which probably led to the adrenal crisis and death as no stress doses of GC were administered. Adrenal suppression has been described after short-time treatment (≤2 weeks) (11, 12), which may have been the case for this patient. In case 2, the long-term GC treatment was abruptly discontinued, most likely due to misunderstanding, and the patient did not receive a stress dose of GC during an infection. Moreover, the patient had abdominal pain and hypotension, which are common symptoms of adrenal crisis. In case 4, the patient should have received IV hydrocortisone when he was not permitted to take oral medications. These cases highlight that sudden discontinuation of GC treatment can lead to an adrenal crisis.

The lesson to be learned from these cases is the importance of obtaining a detailed drug history. First, on admission, it is important to inquire about current medications and medications that have recently been discontinued. Secondly, in long-term GC users, it is necessary to document the need to return to the normal dose of GC following a temporary increase in GC dosage (e.g. due to a chronic obstructive pulmonary disease exacerbation, allergic reaction, or gout attack). Lastly, when all oral medications are suddenly discontinued due to fasting, essential medications such as GC should be administered via alternative routes.

### Administration of GC stress dose

Stress dose administration is essential to prevent adrenal crisis and death during intercurrent illness (5, 13). In case 3, the patient should have received stress doses of GC directly upon admission. Similarly, in case 5, the patient needed a higher dose than 2.5 mg of prednisolone per day during his intercurrent illness.

The awareness of GC-induced adrenal insufficiency continues to grow. During the last few years, three review articles have been published (7, 13, 14), and

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the European Society of Endocrinology has published recommendations concerning stress doses for GC users during infection with the COVID-19 virus (15). Such guidance is important and necessary: a survey showed that 71% of physicians and specialist nurses changed their management of adrenal insufficiency after being directed to the guidelines (16).

In 2020, Simpson *et al.* (17). published guidance on the prevention of adrenal insufficiency and the emergency management of patients presenting with the condition. As reported in these guidelines, two deaths and six severe harms caused by adrenal insufficiency were identified in a database of patient safety incident reports (the National Reporting and Learning System) in the UK (17). Multiple themes were presented, including failure to increase GC doses in surgical stress, inadequate practices regarding medication at admission and discharge, delayed administration of prescribed GC doses, and missed or delayed alternative administration routes in fasted patients (17). Our findings illustrate these themes well.

In the current study, we decided to choose sepsis as the recorded cause of death because sepsis and adrenal crisis share several clinical symptoms and signs, and infections are also one of the leading causes of adrenal crisis (1). Moreover, GC users have increased mortality due to infections. A previous analysis of our study group showed increased mortality in GC users from sepsis with an adjusted hazard ratio (HR) of 2.1 (95% CI 1.9–2.3) compared to non-users (9). The present study indicates that GC-induced adrenal insufficiency may contribute to the increased mortality observed in our previous study.

Other studies indicate that GC withdrawal or GC-induced adrenal insufficiency is underdiagnosed. Incidence rates of hyponatremia, hypotension, gastrointestinal symptoms, and hypoglycemia are increased during the withdrawal period (1 month before and after cessation of GC treatment) compared to before GC treatment was started, according to a Danish population-based study (18). The 47 patients in our study had significantly lower GC doses prior to admission, lower blood pressure on admission, and higher rates of gastrointestinal symptoms and hypoglycemia compared to the patients whose death was likely not related to adrenal insufficiency. All of these clinical features are common in patients with adrenal crisis (1). Low GC dose prior to admission could be a risk factor since these patients had an inadequate GC dose during intercurrent illness. Moreover, 48% of patients receiving long-term treatment with low-dose (5 mg) prednisolone treatment have adrenal insufficiency (19). This highlights the importance of stress dose administration in patients receiving low-dose GC.

Our previous study showed that of all individuals who were dispensed oral GCs in Western Sweden between 2007 and 2014, 55.6% were women (8), whereas in the current, study 60% were men. The reason is that the mean age of patients in this study is 76 years, which is when GC prescriptions become more common in men than in women (8).

Due to various comorbidities and high age, most patients in our study had short life expectancies. However, adrenal insufficiency caused by GC should not contribute to premature mortality in this patient population. Despite the increased rate of adrenal crisis incidence with age, with the highest incidence in patients over 60 years of age (20), GC-induced adrenal insufficiency does not just affect patients with high morbidity. There have been alarming case reports of children who have died or nearly died due to GC-induced adrenal insufficiency (21). Awareness and knowledge of GC-induced adrenal insufficiency are essential and lifesaving.

The main limitation of our study is that it is based on a subjective analysis of medical records without a clear confirmation of adrenal insufficiency. Conducting a study to determine if the recorded cause of death is accurate is a methodological challenge. Our hypothesis was that GC-induced adrenal insufficiency is an overlooked cause of death in GC users. As we did not have blood samples from the patients, we were unable to measure the levels of cortisol in plasma. Instead, we examined medical records for patients where the recorded cause of death was sepsis, since sepsis and adrenal crisis share many symptoms, and infection is one of the most common causes of adrenal crisis. This method has limitations since it is impossible to be 100% certain that adrenal insufficiency was the cause of death. Nevertheless, a retrospective study is probably the only method to investigate this topic. Another limitation is that we only included patients treated with oral GCs. Therefore, patients using other routes of administration, such as GC inhalation, topical, and injection, were not included. The number of individuals at risk of GC-induced adrenal insufficiency-related death is therefore probably underestimated. The main strength of our study is that three experienced investigators reviewed all suspected medical records in a blinded process.

It is necessary to conduct further research in order to determine whether GC users and health-care providers have sufficient knowledge about GC stress doses during intercurrent illnesses. The need for clinical guidelines for the management of GC-induced adrenal insufficiency is urgent and the evidence regarding when hydrocortisone treatment is indicated is lacking (14).

There are unanswered questions regarding how to improve the safety of patients taking GCs. Long-term GC users might benefit from a steroid emergency card. Moreover, a warning signal in an electronic medication management system could be useful if a physician were to accidentally interrupt long-term GC treatment.

## Conclusion

This study shows that GC-induced adrenal insufficiency is likely a neglected cause of premature death in GC users. The awareness of the disorder during intercurrent illness and following cessation of GC treatment is vital for this group of patients.

**Declaration of interest**

GJ has served as a consultant for Astra Zeneca, Novo Nordisk, and Takeda/Shire; he has received lecture fees from Novo Nordisk, Pfizer, and Takeda/Shire (all outside this work). MJE, PT, and OR declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.

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**Data availability**

Data are not publicly available due to ethical reasons. Further inquiries can be directed to the corresponding author.

**Author contribution statement**

All authors contributed to the study design. OR supervised the study. In reviewing medical records, all authors participated as investigators. MJE had full access to data in the study and performed the statistical analysis. GJ and MJE obtained funding. MJE and OR drafted the manuscript and all authors revised it. All authors approved the final manuscript. OR and MJE are guarantors.

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