Chronic Corticosteroid-Induced Adrenal Insufficiency - Prevalence, Symptoms, Identification and Prevention

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To enter the Q&A and polling questions for this activity, go to ascp.com/qa and click on the title of this activity, as seen below.
Speaker Information – Biography

- Tsuhua Susan Chen, PharmD, RPh, MS, BCGP, As a staff pharmacist, clinical-staff pharmacist, pharmacy director, MTM pharmacist, and president of Medication Therapy Management Inc. P.C. since 2012.

Disclosure – Tsuhua Susan Chen

- I have no actual or potentially relevant financial relationship to disclose and no conflict of interest in relation to this presentation
Learning Objectives

• Discuss the prevalence/incidence of chronic corticosteroid use and indication.
• Compare and contrast adrenal crisis (AC), primary (PAI), and Secondary or Tertiary adrenal insufficiency (SAI/TAI) including their clinical presentations and treatment
• Describe the potential clinical situations to cause secondary adrenal insufficiency and adrenal crisis.
• Apply knowledge learned to case study of adrenal crisis, secondary adrenal insufficiency by identifying clinical situations, symptoms and signs, and laboratory test interpretation.
• Apply the pharmacist’s role in corticosteroid (CS)-induced adrenal insufficiency (CSIAI).

1. What type (s) of adrenal insufficiency is(are) corticosteroid-induced?

A. Primary AI
B. Secondary AI
C. Tertiary AI
D. Adrenal Crisis
Prevalence of Corticosteroid Use in USA

• About twenty-nine percent of the patients who take oral corticosteroids had more than five years of usage with mean duration over 1600 days and prevalence is 1.2% of US adults in a ten-year period of time (1999-2008)

• Economic impact: healthcare cost of high-dose corticosteroid patients is about three times that of non-corticosteroid patients


Treatment with Corticosteroids

• Allergic conditions: asthma, rhinitis, hypersensitivity
• Chemotherapy: antiemetic, brain tumors, multiple myeloma
• Autoimmune: hepatitis, Lupus nephritis, rheumatoid arthritis, Crohn’s disease, ulcerative colitis, immune thrombocytopenia, giant cell arteritis
• Respiratory: COPD, acute respiratory distress syndrome, asthma
• Rheumatoid collagen disorders: dermatomyositis/polymyositis, bursitis, tenosynovitis, arthritis (acute gouty)
• Genetics: Duchenne muscular dystrophy
• Rare: multiple sclerosis, eosinophilic esophagitis, adrenal crisis, adrenal insufficiency, Cushing’s disease after treatment, primary adrenal insufficiency, septic shock, spinal cord injury, bell’s palsy, pericarditis, polymyalgia rheumatica, etc.
Types of Adrenal Insufficiency-Primary

- **Primary (PAI):**
  - Most autoimmune cases (90%), such as Addison’s disease.
  - Others are adrenal hemorrhage (antiocoagulants, trauma), infection (TB,HIV)(5%), tumors/cancers (0-33%), drugs-induced (ketoconazole, mitotane, phenytoin, phenobarbital, St. John’s Wort, etc. Directly involving cortisol metabolism), and genetics, etc.
- **Lab tests:** elevated ACTH (300 ng/L) or > 2 fold of UNL plus low cortisol (<5 mcg/dl)
- **Clinical presentation:**
  - Acute: salt wasting, salt craving, hyponatremia, hyperkalemia, volume depletion, and hypotension, fatigue, weakness, and weight loss
  - Long-term: depression, memory loss, hyperpigmentation
Types of Adrenal Insufficiency-Secondary

• Secondary adrenal insufficiency (SAI)
  Diseases or conditions that will affect the function of pituitary glands, therefore affect ACTH and other pituitary hormones. Examples are resection of pituitary tumors, trauma, radiation, leukemia, infections, genetic disorders (cortisol-binding globulin deficiency), HPA suppression and cessation of corticosteroid therapy. Previous including CS-induced AI

• Lab tests, ACTH stimulation test: low ACTH (<10 ng/L or pg/dl) and low cortisol (<18 mcg/dL)

• Clinical presentation: pituitary hormone deficiency, such as amenorrhea, hypothyroidism, headache, visual defects, less hyperpigmentation and hypotension than PAI

Types of Adrenal Insufficiency-Tertiary

• Tertiary (TAI): Most cases of AI, caused majorly by use exogenous corticosteroids that negatively feedback inhibit the hypothalamus and pituitary glands, and lead to HPA axis suppression. Other causes are hypothalamic tumors, surgery, and infection (TB, etc.)

• Lab tests: Low CRH, Low ACTH and low cortisol

• Clinical presentation: similar to SAI

• Recovery: most short-term high dose corticosteroids induced HPA axis suppression can recover within short period (2-3 weeks) with corticosteroid naïve individuals.
Types of Adrenal Insufficiency (AI)-Adrenal Crisis (AC)

- **Causes:** stressors, such as infection, trauma, surgery or inflammation on top of pre-existing adrenal insufficiency could lead to AC. PAI has higher chance to cause AC then TAI/SAI
- **Incidence:** 6-8 /100 patient-year
- **Symptoms:** hypotension (<110 mmHg systolic), syncope, fast heart rate, volume depression (dehydration), may have GI pain, lower chest, back pain, fever (66%), no appetite, N/V, diarrhea alternating with constipation, confusion, very weak, tired, and coma (42%), hypoglycemia

### Treatment of Adrenal Crisis and CSIAI

- **Treat with hydrocortisone:** AC (with stress dose); AIs (low dose)
- **Treatment of AC**
  - Should start in any suspected critically ill patients
  - Taper down rapidly (over 3-4 days)
- **BUT** if patient has pre-existing hypopituitarism, AI, or due to HPA suppression, convert to maintenance dose and taper down schedule needs to be based on individual adrenal function; since adrenal function could take longer time (9-12 months or longer) to recover for chronic CS use patients.
Sick Day Rules-Treatment of AI

- Sick day rule 1: double the routine oral CS when the patient experiences fever or illness requiring bed rest; when requiring antibiotics for an infection; or before a small outpatient procedure (e.g., dental work).
- Sick day rule 2: need to inject a CS preparation i.m. or i.v. in case of severe illness, trauma, persistent vomiting, when fasting for a procedure (colonoscopy!), or during surgical intervention.

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**CS Replacement Based on Surgical Levels**

<table>
<thead>
<tr>
<th>Surgical/illness Levels</th>
<th>CS Replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>During minor surgery or illness</td>
<td>↑ up to 3 times usual dosage for 3 days, rapid taper within 1-2 days; do not change MC dose</td>
</tr>
<tr>
<td>Uncomplicated, outpatient dental procedures under local anesthesia and most radiologic studies</td>
<td>No extra supplementation</td>
</tr>
<tr>
<td>Moderately stressful procedures (e.g., barium enema, colonoscopy, or arteriography) (general anesthesia)</td>
<td>100mg IV dose of HC just before procedure</td>
</tr>
</tbody>
</table>
## Clinical Presentations of AIs

### Acute symptoms

PAI contributes more AC cases than SAI/TAI
- Hypotension (<110mmHg systolic) and syncope/ shock (>90%); volume depression
- Non-specific symptoms:
  - Gastrointestinal symptoms- abdominal pain
  - Fever, no appetite, nausea, vomiting
  - diarrhea/constipation alternating, neuropsychiatric symptoms- confusion, lethargy, disorientation, coma

### Chronic Symptoms

<table>
<thead>
<tr>
<th>PAI</th>
<th>SAI/TAI (CSIAI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric:</strong> (e.g. memory impairment, depression, anxiety, psychosis, reduced consciousness, delirium); Skin: hyperpigmentation and dry</td>
<td><strong>Hypoglycemia</strong></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Sudden severe headache, loss of vision or visual field defect</td>
</tr>
<tr>
<td>Orthostatic hypotension postural dizziness</td>
<td>Orthostatic hypotension postural dizziness</td>
</tr>
<tr>
<td>Salt craving</td>
<td>Salt craving</td>
</tr>
<tr>
<td>Autoimmune manifestations (vitiligo)</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Decreased axillary and pubic hair, loss of libido in females, amenorrhea, premature ovarian failure</td>
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<tr>
<td>Low grade fever</td>
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</tr>
</tbody>
</table>
Other Laboratory Findings

- PAI: hyponatremia, hyperkalemia, metabolic acidosis (decreased bicarbonate)
- Anemia, lymphocytosis, eosinophilia
- Erythrocyte sedimentation rate increased (inflammation markers)
- Elevated TSH normal T4 (PAI)
- Transient elevated ACTH

2. What is Prevalence of SAI/TAI?

A. One out of million
B. 150-280 out of million
C. 1500 out of million
D. Need more information
CS-Induced AI (SAI/TAI)-Prevalence/Incidence

- **Prevalence:**
  - Most cited studies estimated from 150-280 cases per million.
  - Iqbal, et al. recent study indicates the prevalence of SAI is 76 cases per million in the general population.

- **Incidence:**
  - 1.1 per 10,000 personal years was reported in inhaled corticosteroid (more than 3 months) caused adrenal insufficiency.
  - Systemic glucocorticoid therapy can range from 13 to 63% with median of AI 37.4% in those studies in less than 4 weeks and less than 5 mg prednisolone or equivalent daily dose.

Alexandradi KI et al, Endotex NCBI 2018 Aug 20
Chabre O et al. Ann endocrinol 2017;78:490-4
Lapi K et al, Eur Respir J 2014;42:79-86
Iqbal K et al. Endocr Connect 2019;1:20-31

Why There is Wide Range of Prevalence/Incidence of SAI/TAI

- Lack of awareness (under diagnosis) : the interpretation diagnostic /screening test results
- Signs/symptoms are non-specific
- Usually rapid recovery within 3-5 weeks (most of cases, CS naïve)
- Individual genetic metabolic characters play an important role
- Concomitant drugs? Drug interactions
- Study duration (e.g., before or after adrenal function recovered?)
- CS naïve? Or non-naïve? Daily doses? Cumulative doses of CS?
3. What are the risk factors of corticosteroid-induced adrenal insufficiency?

- A. Stressors
- B. Duration of the corticosteroid use
- C. Cumulative doses, and daily doses of corticosteroid use
- D. Genetics and age
- E. All of the above

Corticosteroid-induced AI-Risk Factors

<table>
<thead>
<tr>
<th>Risk Factors of Corticosteroid-Induced Adrenal Insufficiency</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden discontinuance chronic corticosteroids or inappropriate discontinuance corticosteroids</td>
<td>Nicolaides NC et al. Glucocorticoid Therapy and Adrenal Suppression. 2018</td>
</tr>
<tr>
<td>After surgical removal of pituitary adenoma</td>
<td>Alexandraki KI et al. Adrenal Suppression. 2018</td>
</tr>
<tr>
<td>Pituitary damage: tumors, surgery, radiation, brain injury, etc.</td>
<td>Alexandraki KI et al. Adrenal Suppression. 2018</td>
</tr>
<tr>
<td>Genes: cortisol-binding globulin deficiency, CYP3A4 enzyme, etc.</td>
<td>Nicolaides NC, Chrousos GP, Charmandari E. Adrenal Insufficiency. 2017</td>
</tr>
<tr>
<td>Autoimmune, inflammation, infection, etc.</td>
<td>Alexandraki KI et al. Adrenal Suppression. 2018</td>
</tr>
<tr>
<td>Oral corticosteroid on top of chronic inhaled</td>
<td>Bonduulapati LN et al. Clin Endocrinol 2016;85:165-9</td>
</tr>
<tr>
<td>Age</td>
<td>Laugesen K et al. 2019 PLoS One 2019 19;14:e0212259</td>
</tr>
<tr>
<td>Concomitant use antibiotics</td>
<td>Laugesen K et al. 2019 PLoS One 2019 19;14:e0212259</td>
</tr>
<tr>
<td>Long-acting, long half life CS, higher bioavailability inhaler</td>
<td>Alexandraki KI et al. Adrenal Suppression. 2018</td>
</tr>
</tbody>
</table>
Adrenal Crisis (Acute Adrenal Insufficiency)

- 36 yo Asian male had been diagnosed with lupus 4 months ago. He had severe joint pain, elevated inflammatory markers, treated with 20-40 mg prednisolone daily and hydroxychloroquine.
- Recently visit to China and Austria.
- Productive cough, blood pressure (110-90/80-60), loss of appetite, loss of weight (5 kg in 2 weeks), night sweat and intermittent high fever, rash, small dark spot on chest and forearms, lower back pain, and diarrhea. Low blood sugar and very weak. Patient also has decreased platelet count 38X10^9/L ml, and dehydrated. Patient did not have food in the past 12 hours. Treated with amoxicillin/clavulanate, vancomycin, and continue prednisolone 20 mg daily. All the bacterial culture (including TB), viral, and protozoa tests negative after empiric antibiotics; but the symptoms mentioned above still not getting better.

Risk Factors for This Case

a. Stressors (emotional, chemicals, infections, inflammation, etc.) could expedite the pre-existing adrenal dysfunction which comes from CS-induced
b. Discontinue or did not get sufficient corticosteroid doses during hospitalization
c. Diseases that could correlated adrenal crisis: autoimmune diseases, Crohn’s disease, cancers, infections, and sepsis, etc.
d. Conditions that will facilitate adrenal crisis symptoms: on diet, dehydration, drugs caused orthostatic hypotension, etc.
e. More than three months of high dose corticosteroids is good enough to suppress HPA axis
4. What potential diseases/conditions that patient might have?

- A. Unknown origin of infection
- B. Adrenal crisis
- C. SAI/TAI due to decrease corticosteroids

Poll: After antibiotic treatment, the patient still has a fever and cough. Culture/laboratory results are negative for bacterial or viral infection. What intervention will you suggest?

To access the polling questions, go to this link: ascp.com/qa and select the "Chronic Corticosteroid-Induced Adrenal Insufficiency - Prevalence, Symptoms, Identification and Prevention" activity, as seen below.
5. After antibiotic treatment, the patient still has a fever and cough. Culture/laboratory results are negative for bacterial or viral infection. What intervention will you suggest?

- A. Wait until confirmed diagnosis, more antibiotics and IV fluid
- B. Cosyntropin stimulation test
- C. Another TB and blood/urine culture to rule out infection of unknown origin
- D. Stress dose hydrocortisone

Poll: In this case, what test would you suggest to the physician to determine if the patient has AI? Note: Diagnosis is pending, all infectious studies are negative.

To access the polling questions, go to this link: ascp.com/qa and select the “Chronic Corticosteroid-Induced Adrenal Insufficiency - Prevalence, Symptoms, Identification and Prevention” activity, as seen below.
6. In this case, what test would you suggest to the physician to determine if the patient has AI? Note: Diagnosis is pending, all infectious studies are negative.

- A. Random cortisol collection to rule out if patient had adrenal crisis
- B. Insulin tolerance test, since it is a gold standard of adrenal insufficiency
- C. ACTH stimulation test
- D. Dexamethasone suppression test

ACTH Tests (Adrenocorticotropic Hormone)

- How: at least 18-24 hours of CS-free period, get basal level of ACTH/cortisol and then injection 250 mcg cosyntropin, collect cortisol after 30 min and 60 min
- Mechanism: mimic the action of ACTH to stimulate adrenal gland function
- Interpretation: AM cortisol ≤ 3-5 mcg/dl or after stimulation ≤ 18 mcg/dl is AI
  Distinguish SAI from PAI: if basal ACTH elevated (>300 ng/L or > 2 fold UNL) and low cortisol after stimulation indicates PAI. If ACTH low (<10ng/L) and low cortisol (≤18 mcg/dl) is SAI/TAI
- Limitation: recent onset SAI could be missed

Alexandraki KI et al, Endotex NCBI 2018 Aug 20
Basal Cortisol/ACTH and Random Cortisol Test

- How: collect blood sample at 9 AM.
- Interpretation:
  - Cortisol < 3 (sometime 5 mcg/dl) is AI
  - ACTH(<10 ng/L) is SAI / TAI. ACTH > 300 ng/L or > 2 fold UNL is PAI.
- Limitation: sepsis patient may show false negative.
- Advantages: apply it when ACTH test not available.
- Use random cortisol (AI: <10 mcg/dl; normal >33 mcg/dl) for critically ill patients.

Case 2

- 79 yr female has chronic asthma, end-stage Parkinson’s disease, type II diabetes, hypertension, constipation, and depression.
- The physician discontinued Advair 500/ 50 (fluticasone/salmeterol) one puff bid due to considering the chronic adverse effects of 25 years corticosteroid use on 1/29/2018. Last inhaled dose was given in March.
- From March to August, patient had been admitted to ER/hospital 4 times with the symptoms of shortness of breath, extreme weakness, low blood glucose (70-80s), low blood pressure (80-100/50-60), and diagnosis of pneumonia (three times in 5 months) and recurrent UTI. She also experienced significant weight loss in the past 5 months (loss 37 lb.). Visit the patient at first day of her pulmonary ward stay.
Case 2 continued...

- Medication: tegaserod 6 mg bidac, metformin 500 mg tid, Levodopa/carbidopa (250/25 mg) 1.25 tab qid, entacapone 200 mg 1 tab qid, pramipexole 0.25 mg, 1.5 tab tid, lansoprazole 30 mg qd, spironolactone 25 mg bid, and Ipratropium/albuterol (0.5/2.5 mg) q6h.

Poll: What is (are) possible sign(s)/symptom(s) of adrenal insufficiency in this case? (select all that apply)

To access the polling questions, go to this link: ascp.com/qa and select the “Chronic Corticosteroid-Induced Adrenal Insufficiency - Prevalence, Symptoms, Identification and Prevention” activity, as seen below.
7. What is (are) possible sign(s)/symptom(s) of adrenal insufficiency in this case? (select all that apply)

A. Shortness of breath, respiratory infection, UTI infection
B. Weight loss unknown reason, extreme fatigue/weakness
C. Hypoglycemia
D. Hypotension
E. All of the above

Diseases/Conditions can Facilitate SAI/TAI Symptoms in This Case

• A. Parkinson’s disease
• B. Asthma/COPD
• C. Chronic UTI
• D. Immobilization
• E. Chronic use of corticosteroid, high dose of inhaled corticosteroids
After the interview with this patient, what is your suggestion to the attending doctor?

- Patient may have SAI/TAI, due to history of chronic use high dose inhaled corticosteroid and currently discontinue the steroid without appropriate taper down.
- Patient has factors that will facilitate SAI, which is asthma (inflammation), depression (emotional stress), recurrent UTI (infection), and Parkinson’s.
- Patient’s symptoms of SAI/TAI: unknown reason weight loss in a short term, low blood pressure, and low blood sugar.

Case continued....

- After the pharmacist’s suggestion, the patient had received stress dose hydrocortisone in the hospital and rapid taper then switched to oral prednisolone. This patient was discharged with prednisone 5mg bid for one week and then 5 mg qd for two weeks, and then 2.5 mg for another one month and then discontinued. Patient did not have ER/Hospital visit for 4 months. Past discharge medication review did not show any oral prednisone from previous hospitalizations; even though high dose injection CS were used to treat exacerbation of asthma during the previous hospitalizations. After this discharge (8/16/18), patient gained back 10 lb. within 4 months.
- In December, four months after last discharge, patient had recurrent respiratory symptoms and readmitted to hospital, this time the cortisol/ACTH basal level was 19.65/174 (normal cortisol 5.27-22.45 mcg/dl and ACTH 9-46 pg/ml).
8. How will you interpret these results?

- A. Recovery from PAI
- B. Patient’s ACTH is too high and could indicate ongoing PAI.
- C. Recovering from CS-induced AI.

Recovery of Adrenal Function

- Patients had 1-10 year of high dose oral GCs takes 9-12 months to recover adrenal function
- Slowly taper down over 1-4 weeks
- Natural SAI/TAI recovery after complete cessation of CS have 4 stages:
  a. Stage I: Low ACTH/ Low cortisol
  b. Stage II: ACTH starts to become normal or most supernormal/cortisol low
  c. Stage III: supernormal ACTH/cortisol normal
  d. Recovered Stage: normal ACTH/normal cortisol
- Other study showed that over 3 years to recover

Braber AL Ney RL, Nicholson WE et al. 1965
Poll: Four months after last discharge from hospital, patient had recurrent respiratory symptoms and readmitted to hospital, this time the cortisol/ACTH basal level was 19.65/174 (5.27-22.45 mcg/dl/9-46 pg/ml or ng/L). How will you interpret these result? According to Braber AL et al. 1965

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• A. Recovery from PAI
• B. Patient’s ACTH is too high and could indicate ongoing PAI
• C. Recovering from CS-induced AI
Summary: Signs and Symptoms of CS-induced Al

- It is reasonable to suspect CS/Al if the patient has risk factors, medication history, signs/symptoms of Al.
  - Common acute: low BP, orthostatic hypotension, low blood sugar, very weak, N/V/D, fever, etc.
  - Long term: depression, anxiety, memory loss, sleep issue, weight loss, skin spots, dry skin, etc.

- Risk factors/comorbidity:
  - Chronic diseases, dehydration, malnutrition, chronic corticosteroid use (inhaled and oral), not inappropriate withdrawal of CS, recurrent infection, high inflammation status, elevated inflammation markers, high dose of corticosteroid, current/chronic stress, sore throat, cold, and use of pain medications (e.g., opioids), etc.

Identification of SAI/TAI

- Most important: medical/medication history review
- Most the symptoms are nonspecific, look at long-terms medications, whole picture, and most complaints are not correlated to laboratory test results.
  - Examples:
    - Complain about pain, no any structure abnormalities or reasons to cause pain.
    - Complain about weight loss, no reason for loss appetite, no findings to cause nausea/vomit/diarrhea.
    - Memory loss-no evidence on MRI or cognition study.

References see previous slides

Alexandraki KI et al, Adrenal Insufficiency. 2018 Endotex
Prevention of CS-induced AI and Dependence

- Population: over 280k, constant chronic CS use patients
- Intervention: treated by oral corticosteroids at least 3 months.
- Design: Self-controlled, compared withdraw symptoms of these patients from 3 months before and 7 months after of corticosteroids therapies.
- Outcomes: the highest risk period time is one month before and one month after the last prescription---rebound AI symptoms were common during this period, especially, orthostatic hypotension and GI symptoms.

Alexandraki Ki et al, Endotex NCBI 2018 Aug 20
Results of Laugensen et al.

<table>
<thead>
<tr>
<th></th>
<th>Syncope</th>
<th>Hypo-</th>
<th>Hypertension</th>
<th>Gastrointestinal symptoms</th>
<th>Hypoglycemia</th>
<th>Negative outcome (erysipelas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>3,568</td>
<td>634</td>
<td>295</td>
<td>6,332</td>
<td>38</td>
<td>1,850</td>
</tr>
<tr>
<td>Reference period</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Risk period 0</td>
<td>0.8 (0.7-0.9)</td>
<td>0.7 (0.6-1.0)</td>
<td>1.5 (0.9-2.5)</td>
<td>1.0 (0.9-1.1)</td>
<td>0.6 (0.2-2.1)</td>
<td>1.0 (0.8-1.2)</td>
</tr>
<tr>
<td>Risk period 1</td>
<td>1.1 (0.9-1.3)</td>
<td>1.5 (1.1-2.0)</td>
<td>2.5 (1.4-4.3)</td>
<td>1.7 (1.6-1.9)</td>
<td>2.2 (0.7-7.3)</td>
<td>1.1 (0.9-1.4)</td>
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<tr>
<td>Risk period 2</td>
<td>1.0 (0.9-1.2)</td>
<td>1.1 (0.7-1.5)</td>
<td>2.3 (1.3-4.3)</td>
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<td>2.4 (0.6-9.5)</td>
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<tr>
<td>Risk period 3</td>
<td>1.0 (0.8-1.2)</td>
<td>0.9 (0.6-1.4)</td>
<td>2.0 (1.0-3.9)</td>
<td>1.5 (1.3-1.7)</td>
<td>NA</td>
<td>1.1 (0.9-1.5)</td>
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<tr>
<td>Risk period 4</td>
<td>0.9 (0.7-1.0)</td>
<td>0.7 (0.4-1.1)</td>
<td>1.7 (0.8-3.6)</td>
<td>1.5 (1.3-1.7)</td>
<td>0.9 (0.1-8.9)</td>
<td>1.1 (0.8-1.4)</td>
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https://doi.org/10.1371/journal.pone.0212259.t003

Risk Factors of Adrenal Insufficiency After Chronic Systemic CS Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratios and 95% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1</td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
</tr>
<tr>
<td>30–49</td>
<td>1</td>
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<tr>
<td>50–69</td>
<td></td>
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<tr>
<td>≥70</td>
<td></td>
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<tr>
<td>Average daily dose in prednisolone equivalents</td>
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<tr>
<td>≤5 mg/day</td>
<td>1</td>
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<tr>
<td>5–9 mg/day</td>
<td>1.13 (1.02-1.25)</td>
</tr>
<tr>
<td>10–20 mg/day</td>
<td>1.76 (1.59-1.94)</td>
</tr>
<tr>
<td>≥20 mg/day</td>
<td>2.26 (2.89-3.73)</td>
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<tr>
<td>Treatment duration</td>
<td></td>
</tr>
<tr>
<td>≤6 months</td>
<td>1</td>
</tr>
<tr>
<td>6–12 months</td>
<td>1.12 (1.01-1.24)</td>
</tr>
<tr>
<td>1–3 years</td>
<td>1.03 (0.92-1.16)</td>
</tr>
<tr>
<td>≥2 years</td>
<td>1.21 (1.07-1.36)</td>
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<td>Cumulative dose in prednisolone equivalents</td>
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<td>≤0.5 g</td>
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<tr>
<td>0.5–5 g</td>
<td>1.35 (1.10-1.41)</td>
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<td>5+ g</td>
<td>2.08 (1.81-2.34)</td>
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<tr>
<td>Use of antibiotics*</td>
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<td>1</td>
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<tr>
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<td>1.49 (1.64-2.05)</td>
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</tbody>
</table>

* Proxy for infection. The antibiotic prescription had to be redeemed up to 30 days prior to an event to count precipitating factor (modelled as a time-varying exposure)

https://doi.org/10.1371/journal.pone.0212259.t004
Prevention of CS-induced AI and Dependence
continued...

• Symptoms of AI (or rebound symptoms of CS withdrawal) peak within 3 months cessation of CS and can last up to 7 months or longer after cessation

• Take into consideration individual differences, such as the duration and doses of corticosteroid usage, use of antibiotics, and age can increase risk of AI during and after CS therapy

• The better way to prevent CS dependence is to have taper down schedule tailored to patient’s personal condition

Additional Ways to Prevent CS-induced AI and Dependence

• Reduce the non-necessary CS use; including OTC products (e.g. skin or allergy conditions)

• Stress coping skills: Just take break and rest

• Consider extending the taper down period according to individual differences, such as age, duration of treatment, daily doses, cumulative doses, antibiotics uses to avoid rebound symptoms

• Monitoring recovery of adrenal function


Nicholas MN et al, 2018; Laugesen K et al. 2019
Alexandraki KI et al. Adrenal Suppression. 2018, Endotext
Bowden SA et al. 2019
Personalized Medicine And CS-induced AI

1. Genetic elements that involve metabolism, biosynthesis of steroid hormones have been studied. Example: Cytochrome CYP3A4 enzymes involved in many drugs as well as corticosteroids metabolism. Weak metabolizer of this enzyme will have higher cumulative concentration in vivo and might have higher chance of dependence.

2. Other enzymes that involve the steroid hormone biosynthesis, transportation, etc.

3. Also consider all other risk factors listed in slide 23.

CS dependence, CS-induced AI, Rebound Symptoms-Mechanism

• Chronic negative feedback inhibition of hypothalamus, pituitary gland (HPA suppression) will lead to No ACTH secretion. Without ACTH stimulation, adrenal gland will atrophy.

• Atrophy of adrenal gland then take longer time to recover, >2 years or longer.

• Inappropriate taper down schedule (e.g. completely discontinue CS therapy before adrenal recovery, too fast taper down or abrupt discontinue) and experience of CS rebound symptoms may cause CS dependence.
Which taper down method do you prefer for patient who use corticosteroids chronically?

Type I: slowly taper down with monitoring adrenal function; Type II: taper down without monitoring; y axis: dose; X axis: time, digital numbers do not reflect the actual dose or time.

Consultant Pharmacists’ Roles in CSIAI

- Identify via comprehensive medication review
- Involve monitor adrenal function; suggest “sick day” or “stress dose” for patient and provider
- Be the resource of patients’ CS therapy history and current regimen
- Monitor adverse/side effects of chronic CS treatment
- Help create protocol and procedure to identify and safe CS withdrawal policy
- Educate other healthcare providers about the personal difference (personalized medicine) impact on adrenal function recovery and CS dependence
- Educate other healthcare providers/patients on the signs/symptoms of CSIAI
- Help de-prescribe medication regimen that treat conditions are secondary to CSIAI
References


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References


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Social Q&A

To access Q&A, go to this link: ascp.com/qa and select the “Chronic Corticosteroid-Induced Adrenal Insufficiency - Prevalence, Symptoms, Identification and Prevention” activity, as seen below.

Chronic Corticosteroid-Induced Adrenal Insufficiency - Prevalence, Symptoms, Identification and Prevention
9:45am – 10:45am
△ Tsuhua Susan Chen

Chronic Corticosteroid-Induced Adrenal Insufficiency
Prevalence, Symptoms, Identification and Prevention

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