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Aerospace Medicine Clinic

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You are the flight surgeon taking care of a 20-yr-old male student pilot candidate who presents to your office with a 3-d history of mild sore throat with rhinorrhea and malaise. The patient informs you that when symptoms started, he began taking over-the-counter medications Nyquil* and Dayquil*, but they were not effective for symptom relief. During your initial evaluation, the history and examination are consistent with an upper respiratory infection currently on the fourth day of symptoms. You prescribe dextromethorphan/guaifenesin combination and oxymetazoline nasal spray. You counsel him on the progressive nature of viral infections and request that he return should symptoms not improve.

Six days later, the patient returns to clinic after being seen by a local urgent care clinic 3 d prior. The patient was prescribed an albuterol inhaler due to onset of a nonproductive cough and shortness of breath. As the patient was having this new complaint and was symptomatic for 10 d, you clinically diagnose the patient with an unspecified lower respiratory tract infection. Your examination and vital signs are within normal ranges and not concerning. You prescribe azithromycin 500 mg and prednisone 60 mg daily for 5 d for the patient's suspected ailment.

- 1. What clinical presentation/diagnosis warrants the need for antibiotics and prednisone?
 - A. Acute bronchitis.
 - B. Pneumonia.
 - C. Acute sinusitis.
 - D. Acute exacerbation of chronic obstructive pulmonary disease.
 - E. Bronchiolitis.

ANSWER/DICUSSION

1. D. Based on the clinical scenario and medications prescribed, a lower respiratory tract infection of unknown etiology is the presumed diagnosis. Symptoms of nasal congestion and sore throat with progression to cough, and then changes on auscultation, may point to the development of lower respiratory tract infection. In most cases, acute bronchitis is self-limited and

does not warrant specific diagnostics or treatment, but rather supportive care and over-the-counter treatment are sufficient.⁹ As the patient did not exhibit signs or symptoms of fever, tachypnea, rales, or parenchymal consolidation, imaging via chest X-ray was not sought, so antimicrobial therapy and prednisone for this patient were not indicated.⁷ However, for a patient with a chronic obstructive pulmonary disease exacerbation, treatment with prednisone and an antimicrobial is considered a standard clinical practice.⁷

- 2. What is the Strength of Recommendation Taxonomy evidence rating for prescribing corticosteroids for patients with acute bronchitis?
 - A. Consistent, good-quality, patient-oriented evidence.
 - B. Inconsistent or limited-quality, patient-oriented evidence.
 - C. Consensus, disease-oriented evidence, usual practice, expert opinion, or case series for studies of diagnosis, treatment, prevention, or screening.
 - D. Opinion of the expert panel.
 - E. There is evidence of harm from the intervention.

ANSWER/DISCUSSION

2. B. A review of common causes of either upper or lower respiratory infections concludes that these infection processes are usually self-limiting with supportive treatment. Although antimicrobial therapy may be deemed necessary, the use of corticosteroids in upper or lower respiratory infections is not warranted as there is either no clear evidence or insufficient evidence to support their use.^{3,7}

Your patient returns 2 d after being prescribed antibiotics and prednisone because his symptoms were not resolving quickly enough, although he reports feeling somewhat better than previous encounters. During this same visit, the patient complains of increased anxiousness and poor sleep quality. You believe it may be secondary to the initiation of prednisone, so

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you decide to change prednisone dosage from 60 mg daily to 20 mg every 8h. You also prescribe zolpidem 10 mg to help with sleep.

As previously mentioned, your patient is becoming more anxious due to thoughts that his acute sickness is preventing him from completing course work and school projects and pursuing pilot training. These thoughts have become more pronounced, and he is ruminating in despair and pity over his current condition. He reports to you that he thought about falling out of a window but denied a plan to commit such an act. The patient also expresses that his classmates and instructor noticed inattentiveness and difficulty with finding words.

The patient's examination again is unremarkable, and the history is not of an immediate concern for danger to self or others, so the patient leaves the office with safety precautions along with a referral to mental health. The patient is seen by mental health upon your request, the initial encounter occurring 3 d after discontinuation of the 5-d course of azithromycin and prednisone. The mental health visit was constructive, with appropriate behaviors exhibited by your patient as reported to you by the treating specialist. The visit concluded with an assessment of adjustment disorder, and the patient was released to self-care; no medications were deemed necessary.

Two days later, your patient presents back to the same mental health specialist after a concerned classmate walks him back to the clinic. According to the mental health provider, the patient had a flat affect, delayed responses to questioning, difficulty completing the intake form, and was pacing the room with questionable internal stimuli. The patient denied any auditory or visual hallucinations and did not have any prominent positive symptoms of psychosis documented; however, hospitalization of the patient was recommended.

- 3. What would be your primary diagnosis of consideration?
 - A. Schizophreniform disorder.
 - B. Schizophrenia.
 - C. Major depression with psychosis.
 - D. Corticosteroid-induced psychosis.
 - E. Bipolar disorder with psychotic features.

ANSWER/DISCUSSION

3. D. The incidence of neuropsychiatric effects from the use of corticosteroids ranges from 2–60%.² According to three clinical reports, severe iatrogenic reactions have occurred in 5% of 122 cases when a corticosteroid was prescribed.¹⁰ The onset of symptoms with corticosteroids could be rapid after the start of medication or within 2 wk, with a median onset of 11.5 d.^{2,10} According to Warrington, there is a range of psychiatric and cognitive signs and symptoms from mild to severe. These symptoms could be agitation, anxiety, or distractibility, secondary to mania, depression, or mixed state.¹⁷ According to

the literature, 33% of patients with corticosteroid-induced psychosis may experience suicidal ideation.¹⁷

- 4. What is the most important risk factor associated with corticosteroid-induced psychiatric symptoms?
 - A. History of psychiatric disorder.
 - B. Dose of steroid.
 - C. Drug interaction.
 - D. Younger age.
 - E. Route of administration.

ANSWER/DISCUSSION

4. B. A dose of 40 mg daily or higher of prednisone or an equivalent dose of another corticosteroid is the primary and most important risk factor. A retrospective study of 14 cases of steroid-induced psychiatric disorders reported depression occurred 35%, mania 31%, psychosis 14%, and delirium 13%.¹⁰ The Boston Collaborative Drug Surveillance program discovered the incidence of psychiatric disturbance increased among hospitalized patients when the dose of steroid was greater than 40 mg; incidence rates were 1.3% for <40 mg, 4.6% for 41-80 mg, and 18.4% for >80 mg.^{1,17} Another common risk factor is being female, but age, route of administration, and a previous history of psychiatric disorder or steroid-induced psychosis were not found to be risk factors.^{11,16,17} Specific to this case report, the patient was prescribed 60 mg of prednisone, which was later changed to 20 mg three times per day. It could be assumed that the patient's anxiousness and inability to sleep were unrecognized manifestations of adverse effects of prednisone, and changing the timing of dosing from once per day to three times per day was ineffective as opposed to reducing dosage or discontinuing the medication.^{2,11,13}

During admission, the patient was diagnosed by in-patient psychiatry with corticosteroid-induced mood disorder and was started on quetiapine 50 mg nightly. The patient's last dose of prednisone was 5 d prior to admission. After starting quetiapine, the patient's sleep improved and the adverse behavioral changes resolved. He had an unremarkable 3-d hospital stay and was discharged on quetiapine 50 mg at bedtime as needed. On follow-up with mental health, the patient's behavioral changes reemerged, so quetiapine was increased to 150 mg at bedtime. Quetiapine was stopped 3 d later due to symptom improvement, and the patient was cleared of acute mental health concerns 7 d later.

- 5. Which medication is NOT recommended for the treatment of corticosteroid-induced psychiatric disturbances?
 - A. Lithium.
 - B. St. John's wort.
 - C. Quetiapine.
 - D. Citalopram.
 - E. Haloperidol.

5. B. St. John's wort is a five-petal flower that has been used medicinally throughout centuries for various ailments, but most notably for the treatment of depression. There is no reported clinical indication for St. John's wort in the treatment of steroid-induced psychiatric symptoms.^{11,13} Lithium, selective serotonin reuptake inhibitors, atypical antipsychotics, and other agents including tricyclic antidepressants and certain antiepileptic drugs may be beneficial and used based on the treating provider's inclination.⁸ Your patient was treated with quetiapine, an atypical antipsychotic. This class of medication is effective in addressing emerging symptoms and should be used in the lowest effective dose for the shortest necessary duration.^{11,13} The antidepressant citalopram is a selective serotonin reuptake inhibitor that can be used for treatment of a number of psychiatric conditions, most notably major depressive disorder and generalized anxiety disorder. Haloperidol could be used, but it has a higher risk of adverse side-effects when compared to atypical antipsychotics.¹³

Due to the diagnosis rendered, your patient underwent further mental health evaluations for aeromedical risk assessment and disposition. During assessment, your patient's appearance was neat, mannerisms were appropriate, and speech was appropriate with good eye contact. Interviews revealed no personal or family mental health history. There was no history of birth defects, use of illicit drugs, excessive use of alcohol, or physical or sexual abuse inside or outside of the home during childhood. The patient was raised in an intact nuclear family, all of whom were high achievers. The patient's mental health review of systems was unremarkable, including no homicidal ideations and no further suicidal ideations. The patient's physical exam was within normal limits during evaluation. Neuropsychological testing revealed a higher susceptibility to emotional problems when compared to both aircrew and the general population. The patient had obsessive traits but did not meet criteria for obsessive-compulsive disorder or obsessive-compulsive personality disorder, which are two distinct diagnoses. According to the Merck Manual, those with obsessive-compulsive disorder have true obsessions and compulsions, and they are stressed by lack of control over their compulsive drive, resulting in intrusive thoughts and repetitive behaviors to reduce anxietyrelated obsessions. Those with obsessive-compulsive personality disorder are preoccupied with order, and their behaviors, values, and feelings are considered acceptable and consistent with their own sense of self.¹⁸ Both can be treated with therapy and/or use of selective serotonin reuptake inhibitors. After complete work-up and consultation with a mental health specialist, the final diagnosis was corticosteroid-induced bipolar disorder, mixed episode with psychotic features and suicidal ideation.

Corticosteroids are a mainstay of treatment for many clinical disorders, with a steady increase in usage over the last two decades, and their effects are a common occurrence.¹¹ Corticosteroids have various roles and desirable effects on human physiology; however, their exact mechanism of efficacy in one patient versus toxicity in another is not completely understood. The postulated mechanisms of corticosteroid adverse effects involve actions at the cellular level, which include bioavailability, receptor activation, and gene expression.¹³ Another theory involves a potential corticosteroid-induced decrease in the levels of corticotrophin, norepinephrine, and beta-endorphin immunoreactivity.^{11,16} The clearest pathophysiological linkage is likely high or chronic dose corticosteroid impact on dopaminergic neurotransmission, negative feedback on the hypothalamic-pituitary axis, and the reduction in serotonin levels, with each having a direct causation on psychiatric manifestations.¹³

According to a study in the American Journal of Psychiatry, 32.2% of patients (N = 6788) with a diagnosis of substanceinduced psychosis, without a prior history of either schizophrenia or bipolar disorder over a 20-yr period, converted to either a diagnosis of schizophrenia or bipolar disorder.¹⁴ Inferring and drawing upon data from this study, as corticosteroids were not specifically included within the study, individuals who used a wide range of mixed or other substances with various dosing had different effects on behavior, resulting in 35% of subjects converting to either schizophrenia or bipolar disorder.¹⁴ This study specifically found that 50% of schizophrenia conversions occurred within 3.1 yr and 50% of bipolar disorder conversions occurred within 4.4 yr.14 The predictors of schizophrenia conversion were preexisting substance use disorder, personality disorder, or eating disorder, whereas predictors for bipolar disorder conversions were anxiety disorder, unipolar depression, or a personality disorder.¹⁴ When applying a three-dimensional risk matrix of the likely medical event (psychiatric disorder), the occupation (pilot), and the probability utilizing the Royal Canadian Air Force stratification, a conversion rate of 50% in 3.1 yr for schizophrenia or 4.4 yr for bipolar disorder point to a >2% per yr conversion rate, which is >6% per yr and 11% per yr, respectively, for each diagnosis.⁶ Your patient has a serious to medium risk of converting to schizophrenia or bipolar disorder, respectively. The complications as implied from literature would be consistent with corticosteroid use on a chronic versus an acute basis.¹⁴

Although the patient experienced a full recovery, the medical board adjudicating this case review decided to aeromedically disqualify him from flying. The board concluded there was unacceptable risk and uncertainty at the time of waiver submission. The diagnosis is disqualifying for all flying class duties due to the potential risk of recurrence, unless a special issuance or waiver is granted based upon gathered medical history and requested documentation in accordance with the Federal Aviation Administration's Guide for Aviation Medical Examiners,⁴ the U.S. Army's Aeromedical Policy Letters,¹⁵ the Navy's Aeromedical Reference and Waiver Guide,¹² and the Air Force's Aerospace Medicine Waiver Guide.⁵

The medical board did acknowledge the diagnosis as ambiguous, as the event may have been iatrogenic in etiology. For consideration of a waiver or special issuance approval, a thorough history with definitive cause and remission of signs and symptoms within a specified time frame are necessary. Further, the need for psychiatric evaluation and neuropsychiatric testing would be indicated for special issuance or waiver consideration. The opportunity for your aviator's return to flying duties may be considered later with an uncompromised clinical outlook and update with a plan for aeromedical risk mitigation.

In conclusion, as corticosteroids are routinely prescribed, it is important to follow clinical guidelines and management accordingly to avoid unintended consequences as displayed in your patient. The presenting illness may have been self-limiting, requiring reassurance to the patient. With more dialogue, expectation management, and collaboration to ease worry and anxiety with the patient, there may have been no need for prescription medications, but rather more time and over-thecounter symptomatic support.

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