The Evidence for and Against Corticosteroid Prophylaxis in At-Risk Patients

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KEYWORDS

• Corticosteroid prophylaxis • Steroid preparation • Allergiclike reaction • Anaphylaxis
• Contrast material • Premedication • Pretreatment

KEY POINTS

- Corticosteroid prophylaxis is commonly used in the United States for the prevention of allergiclike reactions to iodinated and gadolinium-based contrast material in patients at highest risk of an allergiclike reaction.
- Corticosteroid prophylaxis causes short-term (24–48 h) hyperglycemia that is on average 40 to 150 mg/dL higher than a patient's baseline and is greatest in diabetics and rarely, if ever, causes hyperglycemia-related complications.
- Corticosteroid prophylaxis has a weak mitigating effect on allergiclike reactions, is unlikely to affect the severity of subsequent reactions, and does not prevent all reactions.
- The number needed to treat with corticosteroid prophylaxis to prevent 1 allergiclike reaction-related death in high-risk patients receiving low-osmolality iodinated contrast material is approximately 50,000.
- In the inpatient population, corticosteroid prophylaxis is likely associated with substantial cost and indirect harm related to length-of-stay prolongation that may exceed the benefits premedication is intended to provide in this population.

INTRODUCTION

Allergiclike reactions to modern low-osmolality iodinated contrast media (LOCM) and iso-osmolality iodinated contrast media (IOCM) are uncommon, occurring after approximately 0.6% of intravenous administrations in the general population.[1,2] Although most are mild[1,2] and consist of limited urticaria, moderate (eg, bronchospasm) and severe (eg, anaphylactic shock) reactions can occur.[1,2] The estimated risk of a severe reaction to LOCM or IOCM is approximately 4 in 10,000,[1] and the risk of death is estimated to be less than 1 in 170,000.[1] These risks are even less for gadolinium-based contrast material (GBCM), in which the reaction rate is approximately 0.05% to 0.33%[3–5] and the risk of death is 0.1 to 2.7 per million.[5]

In the United States, patients who are considered at highest risk of an allergiclike reaction to contrast material are often given corticosteroid prophylaxis. This prophylaxis usually consists of a 12- or

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13-hour multidose regimen with or without diphenhydramine. Prophylaxis is given before contrast material administration because (1) it is considered the standard of care in the United States for patients at highest risk (eg, prior moderate or severe allergiclike reaction), (2) there may not be an adequate imaging alternative (ie, contrast material for a particular examination is deemed necessary), (3) switching contrast agents within a class of substances (eg, from one LOCM or IOCM to another, or from one GBCM to another) has been incompletely studied, and (4) corticosteroid prophylaxis is considered a low-risk intervention.[6,7]

In other countries, corticosteroid prophylaxis is not commonly administered because (1) there is no level I evidence that prophylaxis reduces mortality, (2) there is no level I evidence that prophylaxis reduces the incidence of moderate or severe reactions to LOCM or IOCM, and (3) there is no level I evidence that prophylaxis reduces the reaction rate in high-risk patients.[8–10] This lack of an international standard highlights differences in how national guidelines are developed, differences in the priorities of national health care systems, and differences in how data supporting and opposing prophylaxis are interpreted. This review summarizes the literature supporting and opposing the use of corticosteroid prophylaxis, describes the evidence base behind different premedication regimens, reviews national guidelines and standards of practice, and compares the known benefits with the potential harms of prophylaxis.

HISTORICAL PERSPECTIVE

Corticosteroid prophylaxis was popularized in the 1980s for the prevention of contrast reactions related to intravenous urography, angiography, and contrast-enhanced computed tomography (CT).[8,11,12] At that time, most intravascular administrations were with high-osmolality iodinated contrast material (HOCM), which had an adverse event rate 4- to 10-fold higher than LOCM and IOCM.[1] Because of the commonality (overall rate, 12.7%) and seriousness (severe reaction rate, 0.22%) of these reactions in the general population[1] and the necessity of iodinated contrast material for diagnosis, determining a way to reduce the incidence of contrast reactions was considered important. Therefore, early experiments with prophylaxis were conducted in the general population and in high-risk cohorts.[8–11]

Premedication of Average-Risk Patients

The 2 trials with the greatest level of evidence supporting prophylaxis for the prevention of contrast reactions were performed in average-risk patients.[8,9] This design decision was presumably made for the first HOCM trial[8] because there was a strong interest in reducing the reaction rate in all patients. When a second trial was conducted with LOCM in the early 1990s by the same group,[9] average-risk patients were used again despite the lower reaction rate of LOCM compared with HOCM. This second study included a much smaller number of patients. Therefore, these 2 trials, although blinded and randomized, do not directly inform the effect size of prophylaxis in high-risk patients receiving modern LOCM or IOCM.

The first of these 2 trials, published in 1987,[8] randomly assigned 6763 average-risk patients to 1 of 3 arms: 32 mg oral methylprednisolone 12 and 2 hours before HOCM, 32 mg oral methylprednisolone 2 hours before HOCM, or placebo. Since that time, the 12-hour and 2-hour methylprednisolone premedication regimen used in these studies has been termed the *Lasser prep* after the first author of these trials (**Box 1**). This study found that the 2-hour regimen did not reduce reaction rates but that the 12-hour regimen significantly did—reducing the rate of aggregate reactions (9.0% vs 6.4%), reactions necessitating therapy (2.2% vs 1.2%), and grade III reactions (0.7% vs 0.2%; eg, shock, bronchospasm, laryngospasm or edema, loss of consciousness, convulsions, lowering of blood pressure, cardiac arrhythmia, angina, angioedema, pulmonary edema). This trial

Box 1
Common premedication regimens

Lasser 12-hour regimen[8,9]
- 32 mg oral methylprednisolone 12 h prior
- 32 mg oral methylprednisolone 2 h prior

Greenberger 13-hour regimen[11,12]
- 50 mg oral prednisone 13 h prior
- 50 mg oral prednisone 7 h prior
- 50 mg oral prednisone 1 h prior
- 50 mg oral diphenhydramine 1 h prior

Emergent/rapid regimen[15]
- 200 mg IV hydrocortisone immediately
- 200 mg IV hydrocortisone every 4 h prior
- 50 mg IV diphenhydramine 1 h prior

Data from O'Malley RB, Cohan RH, Ellis JH, et al. A survey on the use of premedication prior to iodinated and gadolinium-based contrast material administration. J Am Coll Radiol 2011;8:345–54.

established that corticosteroid prophylaxis was efficacious in the prevention of minor and severe HOCM reactions in average-risk patients. Limitations of the trial included conflation of allergiclike and physiologic reactions and the inclusion of average-risk patients.

The second of these 2 trials, published in 1994,[9] randomly assigned 1155 average-risk patients to 1 of 2 arms: 32 mg oral methylprednisolone 6 to 24 hours and 2 hours before LOCM or placebo. Methylprednisolone significantly reduced the overall (4.7% vs 1.7%) and mild (1.9% vs 0.2%) reaction rates, but the differences in moderate and severe reaction rates were not significantly different. This trial established that corticosteroid prophylaxis was efficacious in the prevention of minor and aggregate LOCM reactions in average-risk patients. Limitations of the trial included conflation of allergiclike and physiologic reactions, inclusion of average-risk patients, lack of standardization of the initial corticosteroid dose, and a failure to show a reduction in moderate or severe reactions. Some argue that this last point was caused by lack of statistical power,[6,9] but to appropriately power such a study likely would require many thousands more subjects given the rarity of severe reactions to LOCM.[1,6]

There is no evidence that premedication reduces the incidence of contrast reactions to GBCM or IOCM in average-risk subjects. Use of premedication in these settings is based on extrapolation of LOCM-based data.

Premedication of High-Risk Patients

Although there is level I evidence that corticosteroid prophylaxis in average-risk patients prevents reactions of all severity to HOCM[8] and prevents aggregate and mild reactions to LOCM,[9] there is no level I evidence that corticosteroid prophylaxis is effective for any contrast medium class in preventing reactions in high-risk patients. High risk is not well defined,[1,7] but most would consider patients with a prior contrast reaction to the same class of contrast media (ie, iodinated or GBCM) to be the highest risk; patients with such a history have an approximately 5- to 6-fold increased risk of a contrast reaction compared with the general population.[1,13] Other risk factors include asthma, allergies to other substances, and other atopic conditions.[1] Importantly, none of these risk factors (including a prior contrast reaction) seems to increase the risk of a future contrast reaction to modern agents by one or more orders of magnitude beyond that of the baseline population.

The efficacy of premedication in high-risk patients was tested by Greenberger and colleagues[11] in 1984 and 1991.[12] In the 1984 study,[11] 563 subjects with a prior adverse reaction to radiographic contrast material underwent 657 contrast-enhanced procedures preceded by 1 of 2 premedication regimens, and reaction rates were compared with historical HOCM controls. The premedication regimen consisted of 50 mg of oral prednisone 13 hours, 7 hours, and 1 hour before contrast material, and 50 mg of oral diphenhydramine 1 hour before contrast material, with or without 25 mg of oral ephedrine. Ephedrine has since fallen out of favor. The 13-hour prednisone and diphenhydramine regimen used in these studies has been termed the *Greenberger prep* after the first author of these studies (see **Box 1**). In the group that did not receive ephedrine, the reaction rate was 9%. That rate compared favorably with the historical control rate cited by the authors (17%–60%) for high-risk non-premedicated subjects receiving intravascular HOCM. This study suggested that premedication may reduce the HOCM reaction rate in high-risk patients. Weaknesses of the study included lack of a control group not given premedication and comparison with historical controls.

In the 1991 study,[12] subjects with a prior adverse reaction to radiographic contrast material underwent LOCM-enhanced procedures preceded by a variety of premedication regimens consisting primarily of 50 mg of oral prednisone 13 hours, 7 hours, and 1 hour before contrast material, and 50 mg of oral diphenhydramine 1 hour before contrast material, with or without 25 mg ephedrine. The reaction rate was 0.7% (1 of 141) for procedures without ephedrine. This study showed that premedication can be used in high-risk patients and is associated with a low LOCM reaction rate. Weaknesses of the study included lack of a control group not given premedication and comparison with historical HOCM controls.

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Emergency Premedication of High-Risk Patients

The strength of evidence for corticosteroid prophylaxis is greatest for the prevention of contrast reactions to HOCM in average-risk patients, less for the prevention of contrast reactions to LOCM in average-risk patients, and lesser still for the prevention of severe reactions to any modern agent in high-risk patients. In each of these scenarios, the dosing schedules that primarily have been tested

are no less than 6 hours in length. The multihour length of the premedication schedule is based on the pharmacology of corticosteroids requiring 4 to 6 hours or more to achieve efficacy.[14] This is likely the explanation for the lack of efficacy of the 2-hour oral regimen studied by Lasser and colleagues.[8] However, some high-risk patients require emergent diagnosis and treatment and cannot wait 12 or 13 hours (eg, inpatients, emergency department patients). In such patients, rapid premedication is sometimes attempted.

The only evidence supporting rapid premedication of high-risk patients is by Greenberger and colleagues,[15] who in 1986 published a case series of 9 high-risk subjects who underwent shorter-duration premedication consisting of 200 mg of intravenous hydrocortisone immediately and every 4 hours thereafter until the procedure was completed, and 50 mg of intravenous diphenhydramine 1 hour before the procedure. No subject had a contrast reaction. This case series showed that a rapid premedication could be used in high-risk patients, but the small sample size and lack of a control group prohibited any determination of efficacy.

The intravenous hydrocortisone and diphenhydramine combination advocated by Greenberger and colleagues[15] is one of the more commonly used rapid premedication regimens in the United States,[16] but there is no evidence base to support its use or that of any other rapid regimen (see **Box 1**).

PRACTICE PATTERNS AND GUIDELINES

Surveys were conducted in 1995 (n = 108 responses)[17] and 2009 (n = 99 responses)[16] of abdominal radiologist members of the Society of Uroradiology to determine the methods and frequency of premedication in use at those times. In 1995, LOCM was still being used selectively at many institutions based on baseline renal function and atopic risk factors, with HOCM being used in subjects considered to be at low risk for renal or immediate adverse events.[17] Corticosteroid premedication was not considered a universal standard, even in patients with a known prior contrast reaction to the same class of contrast media.[17] This was because in such patients, switching from HOCM to LOCM was a common method of reducing the allergiclike reaction risk, and premedication was considered by some to be redundant.[17]

In 2009,[16] at a time in which LOCM/IOCM had virtually replaced HOCM for intravascular use, radiologists had lost the ability to move away from HOCM in at-risk patients. Despite the lack of interval data confirming efficacy of prophylaxis for high-risk patients receiving LOCM/IOCM, the gradual elimination of HOCM for contrast-enhanced studies correlated with a significant ($P<.001$) increase in the use of premedication, even as the risk profile of contrast media improved.[16] This is likely explained by radiologists feeling a need to take action in at-risk patients, even though premedication had still not been shown to reduce severe reaction rates in high-risk patients receiving LOCM/IOCM. **Box 2** shows the usage of premedication in the United States circa 2009.

The most recent iteration of the American College of Radiology's Manual on Contrast Media v.10.1[7] states that the "primary indication for premedication is pretreatment of 'at-risk' patients who require contrast media. In this context, 'at risk' means at higher risk for an acute allergic-like reaction." The manual[7] does not specify a definition of *at risk*, but leaves that decision up to the individual provider. This vague language, heterogeneous opinions about the efficacy of corticosteroid

Box 2
Premedication in the United States c.2009

Greater than 90% would premedicate or not give contrast material for a prior contrast reaction to the same class of contrast material consisting of:

- Many hives
- Bronchospasm
- Facial edema
- Laryngeal edema
- Anaphylaxis

Approximately 30% to 70% would premedicate or not give contrast material for:

- Prior contrast reaction, same class, 1-2 hives
- Severe food or medication allergies
- Asthma treated with multiple medications
- Symptomatic asthma

Less than 20% would premedicate or not give contrast material for:

- Hay fever
- Mild food or medication allergies
- Mild stable asthma

Data from O'Malley RB, Cohan RH, Ellis JH, et al. A survey on the use of premedication prior to iodinated and gadolinium-based contrast material administration. J Am Coll Radiol 2011;8:345–54.

prophylaxis, and medical-legal considerations all likely contribute to the many variations in prophylaxis policies across the United States.[16] Both the Lasser and colleagues[8,9] and Greenberger and colleagues[11,12] protocols are listed in the manual as equivalent options for elective use (see **Box 1**), whereas the rapid protocol shown in **Box 1** is considered in the manual to be preferred for emergency use.[7]

The most recent iteration of the European Society of Urogenital Radiology (ESUR) Guidelines on Contrast Media v.9.0[10] states that "for patients at increased risk of a reaction," one may "consider the use of premedication. Clinical evidence of the effectiveness of premedication is limited and premedication may not prevent anaphylaxis." The ESUR guideline[10] specifies that the following risk factors signify patient-level risk: previous moderate or severe acute reaction to an iodine-based contrast agent, unstable asthma, and atopy requiring medical treatment. Prior acute reactions to GBCM and prior mild acute reactions to iodinated contrast material are not listed among the risk factors by the ESUR, suggesting that the ESUR does not consider premedication to be necessary for either. The ESUR guidelines[10] also include moderate or severe physiologic reactions (eg, vasovagal) as a potential indication for premedication, whereas the American College of Radiology guideline does not think this is necessary.[7] The premedication regimen suggested for elective use by the ESUR is the Lasser prep (see **Box 1**); no emergent option is listed.

NUMBER NEEDED TO TREAT

In average-risk subjects receiving the 12-hour Lasser prep before HOCM administration, the number needed to treat in the 1987 Lasser trial[8] was 34 to prevent a reaction of any severity, 59 to prevent a grade I reaction, 114 to prevent a grade II reaction, and 114 to prevent a grade III reaction. However, these data are not directly applicable to modern practice because that trial studied the effectiveness of prophylaxis in average-risk patients and used HOCM that is no longer used for intravascular administration. Given the failure of the 1994 Lasser trial[9] to show a significant reduction in moderate or severe reactions to LOCM after premedication of average-risk patients, the rarity of moderate and severe contrast reactions to LOCM/IOCM,[1] and the occurrence of breakthrough reactions despite premedication,[13,18,19] if prophylaxis does have a mitigating effect on severe or lethal contrast reactions, the number needed to treat to achieve this is likely very high.

This concept was explored by Mervak and colleagues[13] in a retrospective cohort study of 1051 subjects premedicated for 1 or more indications before contrast-enhanced CT. Using data from their study and historical controls, the number needed to treat was calculated (**Box 3**). To prevent 1 severe reaction in subjects with a known prior iodinated contrast reaction, the number needed to treat with corticosteroid prophylaxis was estimated to be 569 (95% confidence interval [CI], 389–1083).[13] In conjunction with data from 2 other studies,[20,21] this computed to a number needed to treat of 56,900 (95% CI, 38,900–108,300) to prevent a reaction-related death.

HYPERGLYCEMIA

Short- and long-term corticosteroids are known to cause hyperglycemia, and this effect is more pronounced in those with altered glucose homeostasis (eg, diabetes mellitus, critically ill patients).[22] Hyperglycemia is sometimes a consideration when the risks and benefits of prophylaxis are considered. In the 2 randomized, controlled trials by Lasser and colleagues,[8,9] serum glucose was not measured as a secondary outcome. Therefore, all of the available data on serum glucose effects are either retrospective or extrapolated from other uses of corticosteroids unrelated to contrast reaction prophylaxis.[23,24]

In a retrospective cohort of 43 outpatient subjects who underwent 46 premedication episodes[23] with the Greenberger regimen (see **Box 1**), the mean increase in serum glucose after premedication was +58 mg/dL in the first 24 hours, +10 mg/dL within 25 to 48 hours, and −2 mg/dL at 49 to 72 hours. The increase was greatest in diabetics (+87 mg/dL vs +27 mg/dL,

Box 3
Estimated numbers needed to treat with 13-hour corticosteroid prophylaxis to prevent 1 allergiclike reaction to iodinated contrast material in patients with a prior iodinated contrast reaction

Any reaction

- NNT: 69 (95% CI: 39–304)

Severe reaction

- NNT: 569 (95% CI: 389–1083)

Lethal reaction

- NNT: 56,900 (95% CI: 38,900–108,300)

Abbreviation: NNT, numbers needed to treat.
Data from Refs.[13,20,21]

$P = .02$), and there was no hyperglycemia-related complication. In a separate retrospective cohort study investigating the inpatient population,[24] 390 inpatient subjects who underwent 390 premedication episodes with either the Greenberger regimen or an intravenous regimen (see **Box 1**) were compared with 844 control subjects. The mean maximum increase in serum glucose after premedication was +81 mg/dL for the premedicated cohort compared with +46 mg/dL for the control cohort. Similar to the data for outpatients,[23] the hyperglycemic effect lasted less than 48 hours, the increase was greatest in diabetics (144 mg/dL [type I diabetes mellitus] vs 108 mg/dL [type II diabetes mellitus] vs 34 mg/dL [nondiabetics]), and there was no hyperglycemia-related complication. These studies show that corticosteroid prophylaxis results in a modest increase in serum glucose that is greater in diabetics (ie, 40–50 mg/dL [general population], 80 to 150 mg/dL [diabetics]) but self-limited, lasts less than 48 hours, and in general does not result in a hyperglycemia-related complication. Limitations of these studies are their retrospective designs and a lack of control over when the serum glucose measurements were obtained.

BREAKTHROUGH REACTIONS

A breakthrough reaction is a contrast reaction that occurs despite corticosteroid prophylaxis.[7,18,19] It has been known since the earliest studies[11,12,15] and trials[8,9] investigating prophylaxis efficacy that prophylaxis does not prevent all contrast reactions. However, it was not until 2001 that this phenomenon was investigated formally.[18] Freed and colleagues[18] analyzed a 6-year retrospective cohort of 52 subjects who had 61 breakthrough reactions. They found that breakthrough reactions were usually mild (76%), of similar severity to the initial/index reaction (80%), and occasionally severe or life threatening (24%). This study found that corticosteroid prophylaxis does not prevent all reactions, the most common reaction manifestation is one that is similar in severity to the index reaction, and prophylaxis likely does not mitigate the likelihood of a future severe reaction. Limitations of the study are its retrospective design, lack of information about the total number of premedication episodes (ie, precluding determination of a breakthrough reaction rate), and the small number of reactions studied.

A larger retrospective cohort with 175 subjects and 190 breakthrough reactions was analyzed in 2009.[19] Similar to the Freed results,[18] breakthrough reaction severity usually was similar to the index reaction (80%); 12% were less severe and 8% were more severe. In subjects with a mild index reaction, breakthrough reactions were usually mild (91%), but in subjects with a moderate or severe index reaction, breakthrough reactions were often moderate (42%) or severe (67%). Fifty-eight of the 175 subjects underwent an additional 197 contrast-enhanced examinations, which allowed calculation of a repeat breakthrough reaction rate (12%). This study confirmed that breakthrough reactions are usually similar in severity to the index reaction and that the repeat breakthrough reaction rate in subjects who have had a prior breakthrough reaction is approximately 12%. Limitations of this study are its retrospective design and a lack of information about the total number of premedication episodes (ie, precluding determination of an initial breakthrough reaction rate).

Mervak and colleagues[13] addressed the problem of the absent denominator in 2015. Rather than selecting their cohort based on a previous breakthrough reaction, they selected their cohort based on premedication episodes. They analyzed 1051 inpatients completing a Greenberger regimen (see **Box 1**) over a 4-year period before LOCM/IOCM-enhanced CT and compared the breakthrough reaction rate they observed with the ordinary reaction rate in the general population. They found that the breakthrough reaction rate was 2.1% in all subjects with a prior contrast reaction, 0.5% in those whose only risk factor was a prior contrast reaction, and 4.7% in those who had both a prior contrast reaction and additional atopic risk factors (eg, asthma, severe allergies to other things). The aggregate rate (2.1%) was modestly lower than the estimated reaction rate of 3.5% in high-risk subjects receiving intravenous LOCM/IOCM without prophylaxis. In subjects premedicated for reasons other than a prior contrast reaction (n = 425), the breakthrough reaction rate was 0%. This study provided indirect evidence that corticosteroid prophylaxis administered to high-risk subjects modestly lowers the reaction rate, showed that breakthrough reaction rates vary based on the indication for premedication, and established the breakthrough reaction rate in a high-risk population. Limitations of the study are its retrospective design and use of historical controls.

These studies on breakthrough reactions help inform the risk-benefit analysis in high-risk subjects. We now know that breakthrough reactions are usually similar to the index reaction and that prophylaxis probably does not mitigate reaction severity.[18,19] Therefore, if a patient presents for a contrast-enhanced study but has previously had anaphylaxis to the same class of contrast media, it is more likely that if a breakthrough reaction

occurs, it will also be severe. Avoidance of contrast material in patients with a prior severe reaction to the same class of contrast material may be preferable to trusting prophylaxis. We also know that the likelihood of a contrast reaction occurring after premedication is approximately 0.5% in patients whose only risk factor was a prior contrast reaction,[13] 4.7% in patients with additional atopic risk factors,[13] and 12% in patients with a prior breakthrough reaction.[19] These rates can be used to inform providers and patients about the probability a reaction will occur with the assumption that if a reaction does occur, it will probably be the same severity as the index reaction.[18,19] Finally, we know that with respect to patient-level benefit, the number needed to treat to prevent 1 severe reaction in a patient with a prior contrast reaction is approximately 569,[13] and the number needed to treat to prevent 1 lethal reaction is likely greater than 50,000.[21] This information can be used to educate providers and patients about the likelihood of individual benefit when prophylaxis is administered.

CORTICOSTEROID PROPHYLAXIS IN THE INPATIENT SETTING

Given that the number needed to treat with corticosteroid prophylaxis to prevent 1 severe or lethal contrast reaction is large, questions are raised about the risk-benefit ratio of prophylaxis in vulnerable patient populations (eg, inpatients). Although outpatients usually receive their premedication for an elective imaging examination at home, inpatients and emergency department patients receive premedication in a high-risk health care environment.[25] Not only is the need for timely diagnosis and management heightened, but prolonged hospitalization is a recognized risk-factor for hospital-acquired infection, morbidity, and death.[25]

The indirect costs and harms of premedication were studied in 2016 with a retrospective matched cohort study of 2829 subjects undergoing contrast-enhanced CT[21]; 1424 subjects were premedicated with the Greenberger regimen for a prior contrast reaction (see **Box 1**), and 1425 subjects were not premedicated. None of the subjects received a rapid regimen. The authors showed that premedicated subjects had significantly longer median time to CT (+25 hours; 42 hours vs 17 hours), significantly longer hospital length-of-stay (+25 hours; 158 hours vs 133 hours), and significantly more hospital-acquired infections (5.1% vs 3.1%) than the non-premedicated control subjects.

Using these and other data in a hypothetical cohort analysis,[21] the authors showed that to prevent 1 reaction-related death with prophylaxis in the inpatient setting, it would cost $131,211,400, prolong length of stay by an aggregate 162 years, contribute 551 hospital-acquired infections, and result in 32 infection-related deaths (**Table 1**). In a best-case scenario sensitivity analysis in which the greatest benefits of premedication were paired with the least harms of premedication, prevention of 1 reaction-related death was anticipated to cost $17,342,939, prolong length of stay by an aggregate 38 years, contribute 55 hospital-acquired infections, and result in 3 infection-related deaths. In all tested scenarios in the sensitivity analysis, premedicating high-risk inpatient subjects resulted in a greater number of lives lost than saved (see **Table 1**).

These findings can be explained by a combination of facts. Allergiclike reactions to contrast material are uncommon,[1] severe reactions are rare,[1] and lethal reactions are very rare.[1] Prophylaxis has an incomplete weak mitigating effect on the allergiclike reaction rate[9,13] and likely does not modify reaction severity.[18,19] These factors combine to predict a large number needed to treat to prevent 1 severe reaction.[13,21] When paired with the low death rate from appropriately managed anaphylaxis (1%[20]), the number needed to treat to prevent 1 reaction-related death is likely greater than 50,000.[21] However, each inpatient premedication regimen has a substantial effect on time to diagnosis (median prolongation in time to CT, 25 hours) and time to discharge (median prolongation in hospital length of stay, 25 hours), which results in a greater risk for hospital-acquired comorbidities.[21] Such risks likely outweigh the marginal benefits of prophylaxis in the inpatient setting.

WHAT THE REFERRING PHYSICIAN NEEDS TO KNOW

- Corticosteroid prophylaxis in high-risk patients remains in widespread use in the United States.
- Corticosteroid prophylaxis does not prevent all contrast reactions.
- The number needed to treat with corticosteroid prophylaxis to prevent 1 death is approximately 50,000.
- Breakthrough reactions are usually similar in severity to the index reaction.
- Hyperglycemia associated with corticosteroid prophylaxis is usually brief (24–48 hours), mild, and unlikely to result in a hyperglycemia-related complication.

Table 1
Summary of estimated indirect effects incurred in the prevention of one allergiclike reaction to iodinated low-osmolality or iso-osmolality contrast material through the pretreatment of high-risk[a] inpatient subjects in a hypothetical cohort using an oral 13-hour corticosteroid regimen

	Cost/Harm Incurred in the Prevention of 1 Inpatient Contrast Reaction		
Outcome	Any Reaction	Severe Reaction	Lethal Reaction
Hypothetical cohort			
Additional hospital length of stay	72 d	593 d	162 y
Additional cost of hospitalization	$159,131	$1,312,256	$131,211,400
Additional hospital-acquired infections	0.7	5.5	551
Additional hospital-acquired infection-related deaths	0.04	0.3	32
Hypothetical cohort, best-case scenario (all variables)[b]			
Additional hospital length of stay	21 d	211 d	38 y
Additional cost of hospitalization	$26,068	$260,014	$17,342,939
Additional hospital-acquired infections	0.08	0.8	55
Additional hospital-acquired infection-related deaths	0.005	0.05	3.0
Hypothetical cohort, worst-case scenario (all variables)[c]			
Additional hospital length of stay	469 d	1670 d	914 y
Additional cost of hospitalization	$1,640,333	$5,843,687	$1,168,737,500
Additional hospital-acquired infections	7	25	4909
Additional hospital-acquired infection-related deaths	0.4	1.5	295

[a] High-risk is defined as having a prior allergiclike reaction to iodinated contrast material.
[b] Best-case scenario estimates (ie, least risk and optimal therapeutic benefit for all variables) are derived from the multivariate sensitivity analysis.
[c] Worst-case scenario estimates (ie, greatest risk and least therapeutic benefit for all variables) are derived from the multivariate sensitivity analysis.
From Davenport MS, Mervak BM, Ellis JH, et al. Indirect cost and harm attributable to oral 13-hour inpatient corticosteroid prophylaxis before contrast-enhanced CT. Radiology 2016;279:492–501; with permission.

- Use of corticosteroid prophylaxis in high-risk inpatients is likely associated with substantial cost and indirect harm related to hospital length-of-stay prolongation.

SUMMARY

Corticosteroid prophylaxis continues to be commonly used in the United States for the prevention of allergiclike reactions to iodinated and gadolinium-based contrast material. However, it has only a weak mitigating effect on allergiclike reactions, is unlikely to affect the severity of subsequent reactions, and does not prevent all reactions. Breakthrough reactions occur, can be life threatening, and are usually the same severity as the index reaction. Premedication to prevent reactions to GBCM and IOCM is not based on evidence but rather on extrapolation of existing weak support for LOCM-based prophylaxis. There is no evidence base to support use of rapid prophylaxis regimens, but they are often given in urgent and emergent situations because of their generally good safety profile and a belief that they may reduce the reaction risk in these patients. The minimum duration of premedication shown to be effective in the prevention of contrast reactions is 12 hours. The number needed to treat with corticosteroid prophylaxis to prevent 1 reaction-related death in high-risk patients receiving intravenous LOCM/IOCM is approximately 50,000. Premedication of inpatients is likely associated with substantial cost and harm because of hospital length-of-stay prolongation; these indirect effects may exceed the benefits of premedication in this population.

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