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An Investigation Into the Evidence Behind Budesonide/Formoterol (Symbicort®) Usage in the Outpatient Setting as Maintenance and Reliever Medication for Asthma

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Abstract

Objective: To review the available scientific evidence behind the use of budesonide/formoterol for maintenance and reliever therapy for the outpatient control of asthma exacerbation.

Data sources: The Medline database was searched using the terms albuterol, asthma, budesonide formoterol fumarate drug combination, exacerbation, formoterol fumarate, guidelines, long acting beta 2 agonist, randomized control trial, reliever, and Symbicort. Articles cited in the 2016 GINA guidelines were also assessed for relevance and included in this literature review.

Methods: Studies evaluating the clinical efficacy of budesonide/formoterol for maintenance and reliever therapy in patients ≥ 12 years old with diagnosed asthma were included. Acceptable study designs included RCTs, retrospective analyses, prospective analyses, and post hoc analyses published in English no earlier than 2002. All titles and abstracts were initially reviewed for relevance. Articles remaining after initial review were divided equally among authors for in-depth review and data extraction. The quality of evidence of each study was assessed using the 2011 Oxford Levels of Evidence table.

Results: Fourteen of the nineteen articles supported using budesonide/formoterol as both a reliever and maintenance medication. Four articles found no difference in time to first severe asthma exacerbation and one article found no significant difference in number of asthma control days.

Conclusions: The evidence of this review supports the use of budesonide/formoterol as both a maintenance and reliever therapy in adults with uncontrolled, persistent asthma. SMART (Single Maintenance and Reliever Therapy) improves a number of asthma control measures, deeming it a favorable option for inclusion in future NHLBI guideline revisions

1 Introduction

Approximately one in twenty people suffer from asthma worldwide (1), with an estimated 250,000 deaths occurring each year as a result of the disease. (2) In the United States alone, about 1.8 million individuals visited the emergency room for asthma-associated issues in 2010. (3) Asthma is defined as a chronic disease characterized by airway inflammation, bronchial hyper-responsiveness, and airway remodeling. Patients with asthma often experience symptoms of coughing, wheezing, sleep disturbances, and difficulty breathing. (4) These symptoms can interfere with normal daily activities resulting in missed time from school and work.

One of the most important goals in asthma management is the prevention of asthma exacerbations. Improvement in asthma management in the outpatient setting can help prevent missed time from work and school, as well as reduce the risk of developing severe asthma exacerbations that can lead to emergency room visits and asthma-related deaths. In the United States, when a patient begins experiencing signs of an asthma exacerbation, the National Heart, Lung, and Blood Institute (NHLBI) guidelines recommend use of a short-acting beta-2 agonist (SABA), regardless of current asthma medications. (5) In contrast, the

Global Initiative for Asthma (GINA) guidelines recommend increasing the dose of budesonide/formoterol combination inhaler (Symbicort Turbuhaler®) for patients already using the combined inhaler for asthma maintenance therapy. (6) Symbicort is the focus of our study because formoterol, the long-acting beta-2 agonist (LABA), offers a fast onset of action similar to SABA medications, but has the added benefit of a longer duration of action. (7) The NHLBI guidelines were last updated in 2007 and a revision of the guidelines to include this therapy option may be needed to promote improved patient care for patients with asthma. The NHLBI released an assessment report on updating current guidelines in 2015. Within this document, the NHLBI expert working group identified the use of budesonide/formoterol as both maintenance and reliever as a topic of literature review for inclusion in future NHLBI revisions. (8) However, this research has not been published to the best of our knowledge.

Our long-term goal is to determine the most effective and reliable method when treating patients experiencing asthma exacerbations in order to improve asthma control and to decrease morbidity and mortality. Our objective is to investigate the current body of evidence surrounding the use of budesonide/formoterol combined therapy for asthma exacerbation management. The GINA guidelines cite evidence supporting the use of budesonide/formoterol as a reliever medication to control asthma exacerbations. Currently, budesonide/formoterol is not used in the United States as a reliever medication because it is not supported by the NHLBI guidelines. The purpose of this research is to evaluate whether or not this type of therapy improves asthma management and should be included in the NHLBI guidelines. We plan to obtain articles through Medline, focusing on randomized controlled trials published after 2002, including those conducted outside of the U.S. Search terms will include: albuterol, asthma, budesonide formoterol fumarate drug combination, exacerbation, formoterol fumarate, guidelines, long acting beta 2 agonist, randomized control trial, reliever, and Symbicort. Articles referenced in the 2016 GINA guidelines will also be reviewed. Our study population will include individuals twelve years and older diagnosed with asthma. Our qualifications for performing this research come from our previous research experience and receiving formal education on NHLBI and GINA guidelines in pharmacy school. Our clinical experience, in both hospital and outpatient settings, also provides a greater insight into this topic area.

There are two primary aims of our research: investigating the safety and efficacy of using budesonide/formoterol as a reliever plus maintenance inhaler and identifying the potential benefits of using this medication compared to traditional SABA plus ICS therapy in managing asthma exacerbations.

Over the past two decades, the prevalence and economic cost of asthma treatment has increased in the United States. (8) There are multiple factors contributing to this. One such factor includes the convenience and efficacy of asthma medications currently offered. It is our hope that our literature review will influence current asthma practice to improve asthma treatment and reduce the growing economic cost associated with its management. Furthermore, we seek to provide the most up-to-date evidence regarding budesonide/formoterol therapy to medical experts.

2 Methods

2.1 Literature Search Strategy

Searches of the Medline database will be performed using the Ovid Medline interface. References of the returned articles will be screened for additional studies not found through Medline searches. Additionally, cited articles from the GINA 2016 guidelines will be included. A total of ten search terms, including both MeSH and free-word, will be used to comprehensively search Medline. Search terms will include: albuterol, asthma, budesonide formoterol fumarate drug combination, exacerbation, formoterol fumarate, guidelines, long acting beta 2 agonist, randomized control trial, reliever, and Symbicort.

2.2 Study Eligibility Strategy

Accepted study designs will include randomized controlled trials, retrospective analyses, prospective analyses and post hoc analyses written in English that were published in or outside the United States after 2002. Study

participants have to be 12 years or older and diagnosed with asthma. Trials have to focus on outpatient management of asthma using budesonide/formoterol as maintenance and reliever therapy. Mono-ethnic studies will be excluded due to poor transferability to the United States population. There will be no limitations placed on study duration, population size, or demographics. However, we will take these factors into account when evaluating the level of evidence for each study.

2.3 Data Extraction Strategy

All articles obtained, using the predefined search terms, will be compiled and a cursory review of each articles title and abstract will be performed to assess appropriateness based on inclusion/exclusion criteria. Filtered articles will then be incorporated into a comprehensive spreadsheet for further analysis. Each of the three authors will be assigned to review one-third of the remaining articles. This will include extracting and recording key study data, such as study design, population, inclusion/exclusion criteria, medications, primary endpoints, and results. A second review of each article will then be performed by a different author so that every study will be reviewed twice. Articles not meeting inclusion/exclusion criteria upon deeper review will be removed during this process.

2.4 Quality Assessment Strategy

The Oxford 2011 Levels of Evidence table will be used to assess the quality of evidence of each study in this literature review. The tool contains five levels of evidence that are based on study question and design. Level of evidence may be adjusted according to study quality, based on the discretion of the reviewing author. Each author will assign a level of evidence for a reviewed article. If a discrepancy results between two authors, then the third author will review the article and make the final decision.

3 Results

Articles for review were found both directly through searching the Medline database and indirectly through NHLBI and GINA Guidelines. Articles were then sorted into two categories, eligible and ineligible, based on title and abstract. Further analysis of full body text was performed with specific eligibility criteria. Refer to Figure 1. Study Selection Flow Diagram.

The primary outcomes in reviewed articles include: time to first severe exacerbation, rate of severe exacerbations, anti-inflammatory effects and lung function, rescue medication use and small airway parameters, risk of severe exacerbation, number of asthma control days, and morning and evening peak of expiratory flow values. Of the total nineteen articles reviewed, fourteen articles supported the use of budesonide/formoterol as both a reliever and maintenance medication. One article found no significant difference in the number of asthma control days in mild-to-moderate asthmatic patients; four articles found no significant difference in the time to first severe asthma exacerbation. A summary of articles reviewed can be found in Table 1. Data Extraction Table.

Table 1. Data Extraction Table.

Citation	Setting/Study Design	Patient Population	Intervention/Comparator	Results	Level of Evidence
2006 (10)	Study spanning 289 centers, 20 countries, out-patient setting. DB, RCT, PG	Participants: 3394; Median age: 42-43; women 61%, men 39%	I: Bud/form 160/4.5 mcg, 1 puff BID + PRN C: Bud/form + PRN (A) terbutaline 0.4 mg or (B) formoterol 4.5 mcg	Intervention prolonged time to first severe exacerbation and lowered the rate of severe exacerbations per 100 patients.	Level 2
2004 (11)	Study spanning 211 centers, 18 countries, out-patient setting. RCT, DB, PG	Participants: 1890; Median age: 43; women 58%, men 42%	I: Bud/form 160/4.5 mcg, 2 puffs QD + PRN C: Budesonide 160 mcg 2 puffs BID + PRN terbutaline 0.4 mg	Intervention prolonged time to first severe exacerbation (p<0.001). NNT to prevent 1 severe exacerbation per year with bud/form compared to budesonide + terbutaline was 5.	Level 2
2005 (12)	Study spanning 246 centers in 16 countries. RCT, PG, OL, ITT	Participants: 2143; Median age: 45; women 59%, men 41%	I: Bud/form 160/4.5 mcg, 2 puffs BID + PRN C: Sal/flu 50/250 mcg, 1 puff BID + PRN salbutamol	Intervention prolonged time to first severe exacerbation (p=0.0051); RRR: 25%. NNT to prevent 1 severe exacerbation per year with bud/form + PRN, 14.	Level 2
2015 (13)	Multicenter study; Asia. RCT, PG, DB	Participants: 114; Median age: 39; women 40%, men 60%	I: Bud/form 160/4.5 mcg, 2 puffs daily C: Bud/form 160/4.5 mcg, 4 puffs daily + PRN terbutaline 0.5 mg, 2 puffs daily	Intervention exerts greater anti-inflammatory effects and better lung function improvement.	Level 2

2012 (14)	Post-hoc analysis of two DB studies	Study(A);Participants: 654; Median age: 42; women 60%, men 40% Study (B); Participants: 447; Median age: 39; women 57%, men 43%	Study (A); Bud/form 160/4.5 mcg, 1 puff BID + 1 of 3 PRNs: (1) Terbutaline 0.4 mg (2) Formoterol 4.5 mcg (3) Bud/form 160/4.5 mcg Study (B); 1 of 3 regimens: (1) Sal/flu 25/125 mcg, 2 puffs BID + PRN Terbutaline 0.4 mg (2) Bud/form 320/9 mcg, 1 puff BID + PRN Terbutaline 0.4 mg (3); Bud/form 160/4.5 mcg, 1 puff BID + PRN Bud/form	Bud/form maintenance and reliever therapy significantly reduced the risk of severe exacerbation.	Level 2
2012 (15)	China, Korea, Taiwan; Posthoc sub-analysis of the COSMOS Study. OL, NB	Participants: 404; Median age: 46.4; women 63%, men 37%	I: Bud/form 160/4.5 mcg, 2 puffs BID + PRN C: Sal/flu 50/250 mcg, 1 puff BID + PRN salbutamol	Intervention prolonged time to first severe exacerbation (p=0.024); RRR: 44%.	Level 3
2012 (16)	Conducted in two centers, 32 general practices. RCT, PG, OL	Participants: 102; Median age: 42.8; women 62%, men 38%	I: Bud/form 80/4.5 mcg, 2 puffs once daily + PRN C: CBP	Morning and evening peak expiratory flow values were significantly higher with Intervention.	Level 3
2011 (17)	69 centers across Spain. RCT, PG, OL	Participants: 654; Median age: 44; women 64%, men 36%	I: Bud/form 160/4.5 mcg, 1-2 puffs BID + PRN C: CBP	Intervention was at least as effective at improving clinical control.	Level 3
2011 (18)	Most nations in Europe. RCT, PG, OL	Participants: 8053; Median age: 48; women 62%, men 38%	I: Bud/form 160/4.5 mcg, 1 puff BID + PRN C: Bud/form 160/4.5 mcg, 2 puffs BID + PRN	No statistical significance between treatment groups in time to first severe exacerbation (p=0.75).	Level 3
2011 (19)	Post-hoc analysis of five large clinical trials. RCT, DB, PG	Participants:13,434; Median age: 38; women 58%, men 42%	I: Bud/form, strength varied, frequency: Q day or BID C: GINA Guidelines	Intervention achieved lower rates of exacerbation and an equivalent or greater level of control in patients compared to an	Level 3

				equivalent or higher fixed dose of ICS/LABA.	
2010 (20)	Retrospective analysis. RCT, DB, PG	Participants: 12,548; Median age: 39; women 58%, men 42%	I: Bud/form + PRN (dose and frequency varied) C: 1 of 3 groups; (1) High dose ICS (2) Same dose ICS/LABA (3) Higher dose ICS/LABA + SABA	Intervention prolonged time to first severe exacerbation.	Level 2
2009 (21)	Netherlands, multicenter study. RCT, OL, ITT	Participants: 102; Median age: 43; women 62%, men 38%	I: Bud/form 80/4.5 mcg, 2 puffs Q evening + PRN C: CBP	No significant difference in the number of asthma control days in mild-to-moderate asthma patients.	Level 3
2003 (22)	37 centers in 6 countries - Germany, Greece, Israel, The Netherlands, Portugal, South Africa. RCT, DB, PG, ITT	Participants: 344; Median age: 42; women 57%, men 43%	I: Bud/form 160/4.5 mcg, 1 puffs BID C: Fluticasone propionate 250 mcg, 1 puff BID	Intervention was more effective in improving lung function, reducing use of reliever medication and improving control - 32% reduced risk of exacerbation.	Level 2
2011 (23)	RCT, OL, ITT	Participants: 1835; Median age: 43; women 60%, men 40%	I: Bud/form 160/4.5 mcg, 1 puff BID + PRN C: CBP	Non-significant difference (p = 0.189) in time to first severe asthma exacerbation	Level 2
2009 (24)	Belgium. RCT, OL, PG	Participants: 908; Median age: 43; women 57%, men 43%	I: Bud/form 160/4.5 mcg, 1 puff BID + PRN C: CBP	Non-significant difference (p = 0.09) in time to first severe asthma exacerbation.	Level 2

2008 (25)	Multicenter Canada study. RCT, OL, PG, ITT	Participants: 1538; Median age: 43; women 60%, men 40%	I: Bud/form 160/4.5 mcg, 1 puff BID + PRN C: CBP	Non-significant difference (p = 0.09) in time to first severe asthma exacerbation or in exacerbation rate.	Level 2
2010 (26)	RCT, DB, PG	Participants: 2866; Median age: 42; women 62%, men 38%	I: Bud/form 160/4.5 mcg, 1 puff BID + PRN C: Bud/form (640/18 mcg per day) + Sal/flu (100/500 mcg per day)	Intervention prolonged time to first severe exacerbation.	Level 2
2006 (27)	International multicenter study. RCT, DB, PG, ITT	Participants: 697; Median age: 38; women 61%, men 39%	I: Bud/form 80/4.5 mcg, 2 puffs daily C: Budesonide 160 mcg 2 puffs daily + PRN terbutaline 0.4mg	Intervention provided a significantly greater increase in morning peak expiratory flow.	Level 2
2006 (28)	RCT, DB, PG	Participants: 616; Median age: 45; women 59%, men 41%	I: Bud/form 80/4.5 mcg, 2 puffs daily or 1 puff BID C: Budesonide 200 mcg 1 puff daily	Intervention provided a significantly greater increase in morning peak expiratory flow (p<0.001).	Level 2

RCT=Randomized Control Trial, DB=Double-blinded, NB=Non-blinded, PG=Parallel-group, ITT=Intention-to-treat, OL=Open-label, I=Intervention, C=Comparator, RRR=Relative risk reduction, NNT=Number needed to treat, Bud/form=Budesonide/formoterol, Sal/flu=Salmeterol/fluticasone, CBP=Conventional best practices, ICS=Inhaled corticosteroid, LABA=Long-acting b2-agonist, SABA=Short-acting b2-agonist

Figure 1. Study Selection Flow Diagram

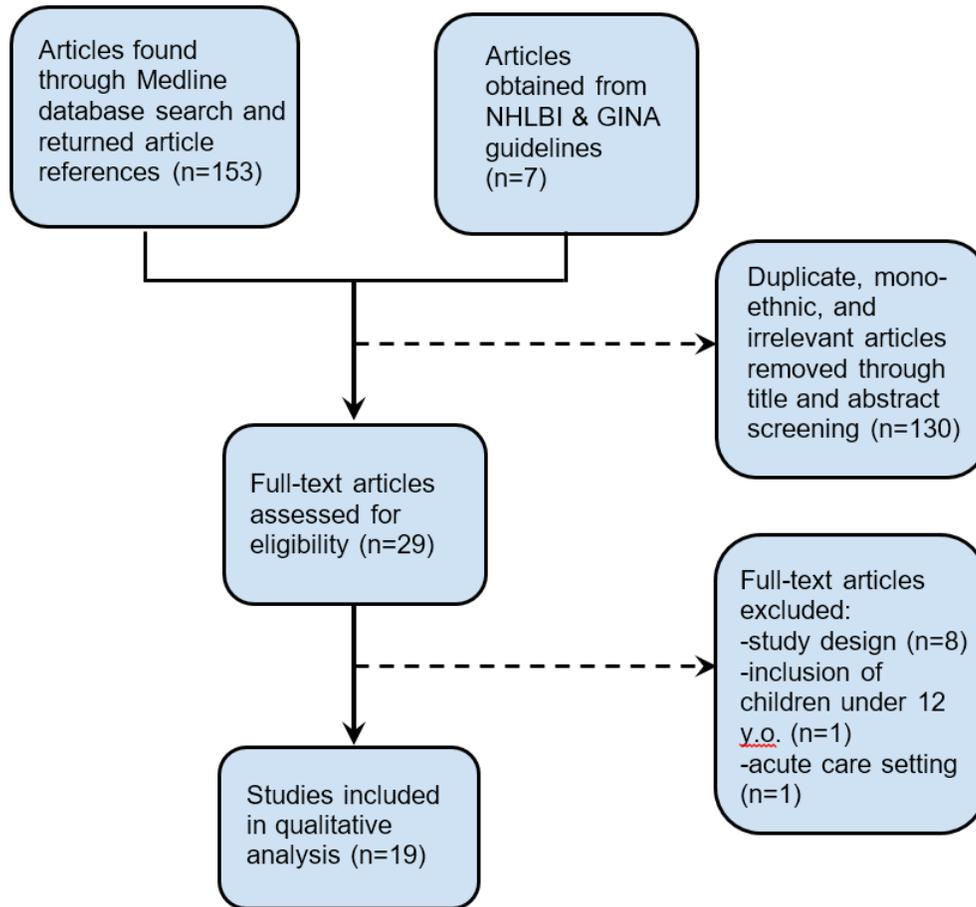


Figure 1: Study Section Flow Diagram

4 Discussion

This systematic review studied the evidence behind using a single inhaler budesonide/formoterol combination for both maintenance therapy and asthma exacerbation relief therapy compared to traditional ICS and SABA therapy for patients over the age of 11. The interest behind performing this literature review comes from the current discrepancy between the United States NHLBI asthma guidelines and the international GINA guidelines with regard to SMART therapy. The 2016 international GINA guidelines have recommended the use of budesonide/formoterol SMART therapy in adult or adolescent patients with one or more yearly exacerbations. Meanwhile, the 2007 NHLBI guideline does not make any recommendation for this type of asthma control therapy. Therefore, we were interested in reviewing available literature to assess current scientific evidence behind using budesonide/formoterol SMART therapy.

An extensive search of Medline literature brought forth eleven studies looking at SMART therapy and its effect on time to first severe asthma exacerbation. Review of the outcomes of these studies found that, in the majority of cases, SMART therapy with budesonide/formoterol prolonged time to first severe exacerbation. Other reviewed studies, focusing on peak expiratory flow (PEF), revealed increased morning and evening PEF values in participants receiving SMART therapy. With regard to asthma control measured in asthma control days, budesonide/formoterol SMART therapy was found to be at least as effective as traditional ICS plus SABA therapy. The combined results of these reviewed studies shows a preponderance of data supporting the benefit of using budesonide/formoterol for asthma control in the outpatient setting.

The results of our review support GINAs recommendation for use of SMART therapy in adolescents and adults with diagnosed asthma. The primary outcomes of all studies reviewed showed non-inferiority or superiority compared to standard therapy. In addition to the efficacy of SMART therapy, our other aim was to investigate the safety of this single inhaler therapy. Our literature review did not uncover any RCTs with safety as a primary outcome measure. Therefore, we feel that more research needs to be performed looking at side effects of SMART therapy. While this is a necessary area of further research, it is worth noting that increased risk of side effects is not expected considering that a majority of reviewed studies reported a significantly decreased ICS dose as a secondary outcome.

4.1 Implications for Practice

The current mainstay of persistent asthma treatment in the United States involves ICS and SABA therapy. Other asthma medications can be added to this backbone therapy or the ICS dose can be increased for improved asthma control. It is from this backbone that most treatment regimens are made. This systematic review points to deviating asthma therapy from this long-standing practice in many patients. The culmination of reviewed articles suggests that the replacement of ICS and SABA with SMART therapy in adolescents and adults with persistent, uncontrolled asthma is beneficial. A major secondary outcome of many of the reviewed studies was reduction in ICS dose with SMART therapy. Therefore, patients with worsening asthma requiring higher doses of ICS therapy may also benefit from SMART therapy. Similarly, SMART therapy reduced rate and time to first severe asthma exacerbation compared to ICS and SABA use. This means that patients on ICS/SABA therapy struggling with frequent asthma flare-ups may find improved control when switching to SMART therapy. In review of the 2007 NHLBI guidelines, we see incorporation of SMART therapy into step 3 of the stepwise approach to long-term treatment of asthma. It is at step 3 that current guidelines recommend increasing to a medium ICS dose or adding a LABA to therapy. Other less common asthma medications, including leukotriene receptor antagonists or theophylline, may be added to a low-dose ICS at this step. This option of adding agents results in an increased medication burden for patients. SMART therapy prevents this burden, as it is a single-inhaler regimen. It also reduces the risk involved with increasing ICS dose. Furthermore, this review shows that switching to this single-inhaler therapy does not sacrifice efficacy, but instead can improve asthma control days and reduce exacerbations in these patients with moderate, persistent asthma. In our minds, this makes step 3 a fitting spot for incorporation of SMART therapy into the NHLBI guidelines.

4.2 Limitations of Study

We have identified a couple limitations of our systematic review. First, only one database was searched. While Medline is a large, extensive database, there is still the possibility that relevant articles were missed because they were housed in a database other than Medline. We felt our knowledge of the Medline interfaces (i.e. PubMed, Ovid) and database size would allow for a practically complete review. Second, the possibility of publication bias, which is the preferential publication of positive results, cannot be discounted. This potential for false positive from publication bias may have been increased by review of literature from the GINA guidelines, which would be using positive findings to support the recommendation of SMART therapy.

The limitations of the studies evaluated should also be discussed. The level of evidence for each reviewed article was assessed using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence. All articles were evaluated by the authors as having a level of evidence of 2 or 3, with the majority receiving

a level 2 appraisal. Overall, this indicates a strong body of evidence pertaining to this topic and provides greater weight to conclusions made from this review. However, study limitations exist regarding study size and open-label study design. These factors contributed to lower level of evidence ratings. There is also the potential issue that these studies were conducted outside of the United States, which may influence the applicability of the results when it comes to the United States population. This risk is mitigated by the fact that the majority of these studies were multinational and involved multiple study centers. However, it would still be valuable for studies to be conducted in the United States to ensure transferability of these results given our patient demographic and asthma treatment nuances compared to other countries.

5 Conclusion

Our review of literature on the use of budesonide/formoterol as both a maintenance and reliever medication found SMART therapy improved multiple asthma control measures, including time to first severe exacerbation, rate of exacerbation, asthma control days, lung function biomarkers, and peak expiratory flow. SMART therapy decreased ICS dose and is associated with reduced medication burden as a single-inhaler treatment option for asthma.

This body of evidence supporting SMART therapy makes it a reasonable alternative to ICS/SABA therapy in adults and adolescents with uncontrolled, persistent asthma. It is our opinion that the available literature found in this review advocates for the incorporation of SMART therapy into NHLBI guidelines.

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