APPENDIX 2

eTable 1. Regulatory limits on total daily dose for asthma medications

Drugs	Canadian max daily dose[i] – Health Canada [1]	US max daily dose[i] – Food and Drug Administration [2]	European max daily dose[i] – European Medicines Agency [3]	UK max daily dose[i] – MHRA [4]
Fluticasone propionate	2000 mcg	2000 mcg	Not available	2000 mcg
Fluticasone furoate	200 mcg	200 mcg	200 mcg[ii]	Not available
Budesonide	2400 mcg	1600 mcg	1600 mcg	1600 mcg
Beclomethasone	800 mcg	800 mcg[iii]	Not available	800 mcg
Ciclesonide	800 mcg	800 mcg[iii]	800 mcg[iii]	800 mcg[iii]
Mometasone	800 mcg	800 mcg	Not available	800 mcg
Salmeterol	100 mcg	100 mcg	Not available	100 mcg
Formoterol	48 mcg	24 mcg	48 mcg	48 mcg
Vilanterol	25 mcg	25 mcg	25 mcg	Not available

i: Maximum dose references were verified March 19, 2016

ii: based on maximum dose of fluticasone furoate in combined fluticasone furoate/vilanterol puffer, as single fluticasone furoate puffer not available

iii By convention, we have listed the dose delivered by the metered dose inhaler valve, whereas US, EMA, and MHRA list a maximum recommended daily dose delivered from the metered dose inhaler actuator, which is 640 mcg (equivalent to 800 mcg delivered by the metered dose inhaler valve)

eTable 2. Summary of Included Studies

Study	Purpose	Studies/Patients Included Relevant to AAP Yellow Zone Formulation	Findings	Citations in Included Guidelines	Relevance to Proposed Yellow Zone Algorithm
Randomized Controlled Trials					
Go, et al. 2010 [5]	Compare nebulized fluticasone to IV hydrocortisone for severe acute asthma exacerbations	33 patients with all levels of baseline asthma severity presenting to the emergency department with severe acute asthma exacerbation	Significant improvements in PEF and FEV1 with nebulized fluticasone compared to IV hydrocortisone	None	Not relevant. Dose not provided, and nebulized therapy not easily available for outpatients.
Systematic Reviews					
Bateman, et al. 2011 [6]	Compare SMART to standard and/or higher fixed dose maintenance therapy for uncontrolled asthma	5 RCTs with 12512 patients. At entry all had uncontrolled asthma at GINA treatment Steps 2 (1037 patients), 3 (6352 patients), and 4 (5123 patients). All patients were using ICS, and 45% were also using LABA	Significant reduction in exacerbation rates with SMART therapy compared to same maintenance dose and higher fixed dose maintenance therapy with ICS/LABA	GINA All included studies also cited in CTS and BTS/SIGN	Not relevant. SMART was not compared to increased ICS in a yellow zone approach
Cates, et al. 2013 [7]	Compare SMART to current best practice	13 RCTs with 13152 patients. Patients	Significant reduction in exacerbations	GINA	Not relevant. SMART was not

	(by GINA guidelines) in patients with persistent asthma	with asthma not well controlled on ICS alone; 82% also using LABA at study entry	requiring OCS and decreased overall ICS dose with SMART compared to current best practice.		compared specifically to step-up therapy in the yellow zone, and details about "current best practices" were not provided
Kew, et al. 2013 [8]	Compare SMART to standard and/or higher fixed dose maintenance therapy for uncontrolled asthma	4 RCTs with 9130 patients. Patients had persistent asthma with at least 1 exacerbation in the last 12 months, on regular ICS therapy and in regular need of rescue therapy; 38-55% also using LABA at study entry	Significant reduction in exacerbations requiring OCS and ER visits with SMART compared to higher fixed dose maintenance therapy	GINA and BTS/SIGN, and all included studies were referenced in CTS	Not relevant. SMART was not compared to increased ICS in a yellow zone approach
Quon, et al. 2010 [9]	Compare doubling the dose of ICS as part of an AAP at the onset of asthma exacerbation to maintaining the current dose of ICS	5 RCTs with 1222 adult patients. Mild to moderate asthma at baseline on ICS. 0-41% also using LABA at study entry	No significant reduction in exacerbations requiring OCS with doubling the dose of ICS compared to continuing the maintenance dose	CTS, BTS/SIGN, GINA	Relevant. Data already accounted for in guideline-based algorithm.
Edmonds, et al.	Compare high dose ICS	4 RCTs with 716	No significant	BTS/SIGN,	Relevant. Trials

2012 [10]	to OCS (tapered dose and maintenance dose) on discharge from the emergency department after acute asthma exacerbation	adult patients. Mild to moderate asthma at baseline. 35-80% of patients on ICS at baseline," "low percentage" also using LABA at entry in all studies	differences in asthma relapse rates or admission with high dose ICS compared to OCS on discharge from the ER after asthma exacerbation	GINA	included provide a potential alternative to OCS in mild to moderate asthma exacerbations when ICS escalation is otherwise limited (see "Additional Rules" section of Algorithm Development)
Edmonds, et al. 2012 [11]	Compare ICS with placebo and with systemic CS for the treatment of acute asthma exacerbation presenting to the emergency department	ICS vs. placebo: 6 RCTs with 478 patients. Mild to severe asthma at baseline. Varied ICS and LABA use at study entry ICS vs. systemic CS: 5 RCTs with 383 patients. Mild to	ICS vs. placebo: 1 study found significant reduction in hospital admission with ICS compared to placebo. All others found no significant difference in outcomes (FEV1 change, hospitalization, Borg scale change) ICS vs. systemic CS: No significant difference in	BTS/SIGN and GINA	Not relevant. Studies were either negative or used a drug not widely used/available (flunisolide) and only involved an extremely short course of therapy (3 hours) in the emergency room Studies were either negative or only involved an

		moderate asthma at baseline. Varied ICS and LABA use at study entry	hospitalization, change in PEF and FEV1, and sputum eosinophil count. Two of the included trials found significant improvements in short term clinical markers (RR, HR, PEF, FEV1) with ICS compared to systemic CS		extremely short course of therapy (3 hours) in the emergency room, with short term physiologic outcome measurement
Practice Guideline					
Dinakar, et al. 2014 [12]	Provide general recommendations for the management of acute loss of asthma control using an AAP	Various	Recommendation advising patients currently treated with daily low-to-moderate dose ICS therapy to quadruple the total ICS dose for acute loss of asthma control in the yellow zone	All included studies referenced in CTS, GINA, BTS/SIGN	Relevant. Data already accounted for in guideline-based algorithm
Narrative Review					
Spaggiari, et al. 2014 [13]	Review the treatments for acute asthma exacerbations	Various	Current evidence does not support the use of ICS as a substitute for systemic CS in the	All included studies referenced in BTS/SIGN and GINA	Relevant. Data already accounted for in guideline-based algorithm

			emergency department		
Bateman, et al. 2013 [14]	Review studies comparing high-dose ciclesonide to other treatments in moderate to severe asthma with and without loss of control	High dose ciclesonide (800mcg BID for 2 weeks) vs. OCS (40mg daily for 2 weeks): 1 RCT with 130 patients with worsening asthma following systematic ICS withdrawal	No significant difference in improvements in morning PEF, asthma symptoms, and FEV1 with high dose ciclesonide compared to OCS in this reviewed trial, no serious adverse event and fever adverse events with high dose ciclesonide	None	Relevant. Provides a safe and effective alternative to OCS in patients on high dose maintenance ciclesonide (shows safety of temporarily exceeding regulatory limit on total daily dose)
Fitzgerald, el al. 2010 [15]	Review methods to gain control of moderate asthma	Various	Quadrupling the maintenance dose of ICS at the onset of an exacerbation may prevent the development of a more severe exacerbation.	All relevant studies referenced in BTS/SIGN and GINA	Relevant. Data already accounted for in guideline-based algorithm

Abbreviations: AAP denotes asthma action plan; BTS/SIGN denotes British Thoracic Society/Scotish Intercollegiate Guideline Network; CS denotes corticosteroid; CTS denotes Canadian Thoracic Society; ER denotes emergency room; FEV_1 denotes forced expiratory volume in one second; GINA denotes Global Initiative for Asthma; ICS denotes inhaled corticosteroid; HR denotes heart rate; ICS/LABA denotes inhaled corticosteroid/long-acting beta agonist; OCS denotes oral corticosteroids; PEF denotes peak expiratory flow; RCT denotes randomized controlled trial; RR denotes respiratory rate; SMART denotes Budesonide/formoterol as maintenance and reliever therapy

APPENDIX 3

Search Strategy

Database: Ovid MEDLINE(R) <1946 to March week 1 2016>
Search Strategy:
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1 Asthma/ (107406)
2 asthma*.tw. (118101)
3 1 or 2 (137050)
4 exacerbat*.tw. (64322)
5 acute.tw. (841712)
6 Emergencies/ (34855)
7 emergenc*.tw. (219845)
8 sever*.tw. (1866724)
9 Status Asthmaticus/ (1058)
10 status*.tw. (541082)
11 cris#s*.tw. (38913)
12 worse*.tw. (121718)
13 attack*.tw. (90593)
14 or/4-13 (3344940)
15 3 and 14 (43834)
16 Budesonide/ (3734)
17 fluticasone.mp. (3318)
18 Beclomethasone/ (2822)
19 ciclesonide.mp. (277)
20 mometasone.mp. (706)
21 salmeterol.mp. (2409)
22 formeterol.mp. (6)
23 laba.mp. (744)
24 (inhal* adj2 corticosteroid*).mp. (7005)
25 long-acting beta2-agonist*.mp. (721)
26 exp Bronchodilator Agents/ (234275)
27 exp Anti-Asthmatic Agents/ (252665)
28 zenhale.mp. (1)
29 symbicort.mp. (143)
30 advair.mp. (40)
31 asmanex.mp. (3)
32 alvesco.mp. (9)
33 qvar.mp. (60)
34 pulmicort.mp. (141)
35 flovent.mp. (20)
36 or/16-35 (257205)
37 15 and 36 (11097)
38 limit 37 to yr="2010 -Current" (2572)
39 limit 38 to (controlled clinical trial or meta analysis or randomized controlled trial or "review" or systematic reviews) (1044)
40 remove duplicates from 39 (972)

41 exp animals/ not (exp animals/ and exp humans/) (4061621)
42 40 not 41 (970)
43 limit 42 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") (371)
44 limit 42 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)") (421)
45 42 not 44 (549)
46 43 or 45 (760)

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Database: Embase <1974 to 2016 March 07>
Search Strategy:
---
1 asthma/ (180791)
2 asthma*.tw. (170702)
3 1 or 2 (217545)
4 disease exacerbation/ (47697)
5 exacerbat*.tw. (97189)
6 acute.tw. (1184791)
7 emergency/ (41092)
8 emergenc*.tw. (327234)
9 disease severity/ (394146)
10 sever*.tw. (2605687)
11 asthmatic state/ (1820)
12 status*.tw. (784549)
13 cris#s*.tw. (54105)
14 worse*.tw. (208162)
15 attack*.tw. (127632)
16 or/4-15 (4802214)
17 budesonide/ (16160)
18 fluticasone/ (6247)
19 budesonide.mp. (17494)
20 fluticasone.mp. (13774)
21 beclometasone/ (6637)
22 beclomethasone.mp. (3548)
23 ciclesonide/ (1164)
24 ciclesonide.mp. (1206)
25 mometasone furoate/ (3614)
26 mometasone.mp. (3738)
27 salmeterol/ (6670)
28 salmeterol.mp. (9490)
29 formoterol/ (4717)
30 formeterol.mp. (33)
31 formoterol.mp. (6477)
32 laba.mp. (1742)

33 (inhal* adj2 corticosteroid*).mp. (11159)
34 long-acting beta2-agonist*.mp. (1858)
35 exp antiasthmatic agent/ (243704)
36 exp bronchodilating agent/ (180379)
37 zenhale.mp. (8)
38 symbicort.mp. (751)
39 advair.mp. (661)
40 asmanex.mp. (123)
41 alvesco.mp. (163)
42 qvar.mp. (371)
43 pulmicort.mp. (1345)
44 flovent.mp. (422)
45 or/17-44 (249081)
46 3 and 16 and 45 (23946)
47 limit 46 to yr="2010 -Current" (8068)
48 (exp animals/ or exp animal experimentation/ or nonhuman/) not ((exp animals/ or exp animal experimentation/ or nonhuman/) and exp human/) (5697975)
49 47 not 48 (7865)
50 limit 49 to embase (7471)
51 limit 50 to (adult <18 to 64 years> or aged <65+ years>) (2205)
52 remove duplicates from 51 (2183)
53 limit 52 to (randomized controlled trial or controlled clinical trial) (376)
54 limit 52 to (meta analysis or "systematic review") (30)
55 limit 54 to "review" (5)
56 53 or 54 or 55 (398)

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Database: EBM Reviews - Cochrane Central Register of Controlled Trials <March 2016>
Search Strategy:
---
1 asthma/ (8386)
2 asthma*.tw. (20014)
3 1 or 2 (20533)
4 disease exacerbation/ (1)
5 exacerbat*.tw. (6307)
6 acute.tw. (63814)
7 emergency/ (1)
8 emergenc*.tw. (10191)
9 disease severity/ (0)
10 sever*.tw. (68078)
11 asthmatic state/ (0)
12 status*.tw. (35470)
13 cris#s*.tw. (1091)
14 worse*.tw. (11410)
15 attack*.tw. (6035)
16 or/4-15 (171901)

17 budesonide/ (1214)
18 fluticasone/ (0)
19 budesonide.mp. (2882)
20 fluticasone.mp. (3055)
21 beclometasone/ (903)
22 beclomethasone.mp. (1785)
23 ciclesonide/ (0)
24 ciclesonide.mp. (372)
25 mometasone furoate/ (0)
26 mometasone.mp. (680)
27 salmeterol/ (0)
28 salmeterol.mp. (1981)
29 formoterol/ (0)
30 formeterol.mp. (27)
31 formoterol.mp. (1679)
32 laba.mp. (259)
33 (inhal* adj2 corticosteroid*).mp. (2588)
34 long-acting beta2-agonist*.mp. (240)
35 exp antiasthmatic agent/ (15070)
36 exp bronchodilating agent/ (0)
37 zenhale.mp. (3)
38 symbicort.mp. (146)
39 advair.mp. (50)
40 asmanex.mp. (4)
41 alvesco.mp. (1)
42 qvar.mp. (30)
43 pulmicort.mp. (143)
44 flovent.mp. (14)
45 or/17-44 (22133)
46 3 and 16 and 45 (2972)
47 limit 46 to yr="2010 -Current" (554)
48 Asthma/ (8386)
49 asthma*.tw. (20014)
50 48 or 49 (20533)
51 exacerbat*.tw. (6307)
52 acute.tw. (63814)
53 Emergencies/ (560)
54 emergenc*.tw. (10191)
55 sever*.tw. (68078)
56 Status Asthmaticus/ (43)
57 status*.tw. (35470)
58 cris#s*.tw. (1091)
59 worse*.tw. (11410)
60 attack*.tw. (6035)
61 or/51-60 (171969)
62 50 and 61 (5963)
63 Budesonide/ (1214)
64 fluticasone.mp. (3055)

65 Beclomethasone/ (903)
66 ciclesonide.mp. (372)
67 mometasone.mp. (680)
68 salmeterol.mp. (1981)
69 formeterol.mp. (27)
70 laba.mp. (259)
71 (inhal* adj2 corticosteroid*).mp. (2588)
72 long-acting beta2-agonist*.mp. (240)
73 exp Bronchodilator Agents/ (12345)
74 exp Anti-Asthmatic Agents/ (15070)
75 zenhale.mp. (3)
76 symbicort.mp. (146)
77 advair.mp. (50)
78 asmanex.mp. (4)
79 alvesco.mp. (1)
80 qvar.mp. (30)
81 pulmicort.mp. (143)
82 flovent.mp. (14)
83 or/63-82 (20098)
84 62 and 83 (2755)
85 limit 84 to yr="2010 -Current" (496)
86 47 or 85 (554)
87 limit 86 to (controlled clinical trial or meta analysis or "review" or "review literature" or review, academic) (9)
88 limit 86 to cochrane airways group (380)
89 87 or 88 (384)

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APPENDIX 4

Exception rules – supplementary information

High Dose Fluticasone

Levy, et al. randomized 413 patients with exacerbations severe enough to warrant oral corticosteroid treatment to either fluticasone 2000 mcg/day or oral prednisolone 40mg daily with a tapering regimen, and demonstrated no significant difference between the two groups in the primary outcome of treatment failure.[16] Twenty percent of patients in the fluticasone group were on a baseline inhaled corticosteroid dose of more than 1000 mcg/day BDP equivalents, and the median baseline dose was 800 mcg/day BDP equivalents (information on LABA use was not provided). As beclomethasone and fluticasone have similar potencies,[17] this suggests that a median dose intensification of only 2.5 times was effective in these patients. Additionally, the baseline dose did not predict treatment failure in a regression analysis.[16] Similarly, Di Franco, et al. randomized 37 patients with asthma exacerbations discharged from the emergency department to receive fluticasone 2000 mcg/day or an oral corticosteroid taper and found no between-group differences in sputum eosinophils, forced expiratory volume in the first second, peak expiratory flow variability, symptom score, or use of rescue medications. Baseline ICS doses ranged from 400-1500 mcg BDP equivalents, with a mean of 785 mcg BDP equivalents. Of note, the majority of patients were also on a LABA.[18]

Moderate and High Dose Budesonide

Fitzgerald, et al. randomized 185 patients discharged from the emergency room after receiving bronchodilators and systemic glucocorticosteroids for an asthma exacerbation to either budesonide 2400 mcg/day or prednisone 40mg daily, both for 7-10 days.[19] Baseline ICS and/or LABA doses were not provided, but roughly half of patients in each group were on an ICS at baseline. Relapse rates and improvements in forced expiratory volume at one second, symptoms, peak expiratory flow and quality of life were not significantly different between groups. Notwithstanding that these patients did receive a dose of systemic steroids, the results may suggest that a sufficiently high dose of budesonide is of similar efficacy to a short course of OCS. A second study by Nana, et al. randomized 81 patients discharged from the emergency room after receiving a single dose of 60mg of prednisolone and bronchodilators to either budesonide 3600 mcg/day or a tapering dose of prednisolone (from 40 to 5 mg per day over 7 days) (again, baseline ICS and/or LABA doses were not provided). Similarly, no between-group differences were found in clinical symptom scores, mean forced expiratory volume at one second increase, or peak expiratory flow increase at 7 day follow-up.[20] Although this was a higher dose than the Canadian allowable daily budesonide limit of 2400 mcg, it supports the role of high dose budesonide, regardless of baseline dose, in controlling severe exacerbations.

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