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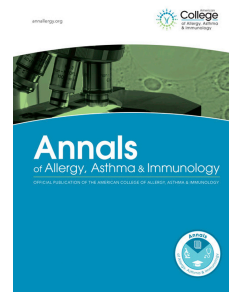
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Use of inhaled corticosteroids in asthma and COVID-19 : Keep calm and carry on

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1 Inhaled corticosteroids (ICS) are used as anti-inflammatory controller therapy given
2 either alone or combination with long acting bronchodilators for persistent asthma .
3 The present COVID-19 pandemic has inevitably focussed attention as to whether ICS
4 might predispose to SARS-CoV-2 infection , especially in older ,male, obese,
5 smokers with comorbidities including chronic lung disease who are prone to more
6 severe COVID-19 infection and worse outcomes. In the later stage of COVID-19
7 infection there is an acute inflammatory cytokine cascade including interleukin 1-beta
8 (IL1- β) , interleukin-6 (IL6) and tumour necrosis factor alpha (TNF- α). This in turn
9 results in a hyper-inflammatory and coagulopathy state with acute respiratory distress
10 syndrome and an attendant high mortality rate. A United Kingdom database of 17
11 million adult patients reported the .presence of asthma without recent oral
12 corticosteroid use was associated with a 10% increased risk of hospital death with
13 COVID-19 , which doubled to 20% in those with recent oral corticosteroid (OCS)
14 use. The present evidence does not support the use of systemic corticosteroids for
15 treating COVID-19. .Although ICS exhibit dose related systemic absorption from the
16 lung the degree of attendant systemic glucocorticoid activity in asthma is relatively
17 low compared to OCS. Whether or not ICS might confer a different risk-benefit
18 profile in COVID-19 is presently unknown . Here we discuss the pros and cons of
19 using ICS in relation to COVID-19 (Figure) .

20 Concerns around the use of ICS in asthma in COVID-19 arise from the potential
21 immunosuppressive effects in the lungs especially in the presence of impaired host
22 defence. The premise here is that corticosteroids may promote viral replication,
23 delayed viral clearance and also predispose to secondary bacterial infection. In
24 support of this a Canadian cohort study of asthma patients demonstrated that current
25 exposure to ICS was accompanied by a 45% relative increase in bacterial pneumonia

26 risk . In contrast a study in H1N1 influenza A infection among 1520 UK hospitalized
27 patients found those with asthma were 49% less likely to require intensive care
28 support or to die than those without asthma , which was attributed to ICS use.
29 This in turn suggests the possibility of a class effect of ICS by protecting against viral
30 insults in asthma patients, which might be due to downstream cytokine suppression .
31 In favour of this hypothesis in vitro suppressive effects were seen with budesonide on
32 replication of coronavirus HCoV-229E (the common cold) and on production of
33 cytokines including IL6 ,IL8 and interferon- β ,using primary cultures of human nasal
34 and tracheal epithelial cells ,while another in vitro study showed systemic suppression
35 of IL6 by budesonide^{1,2}. This could be particularly relevant as raised levels of IL6 are
36 strongly related to worse outcomes in patients with severe COVID-19 pneumonia
37 with evidence of hyper-inflammation. In addition it has been shown that in sputum
38 cells from 330 asthma patients the use of ICS was associated with reduced gene
39 expression of angiotensin converting enzyme 2 (ACE2) and transmembrane serine
40 protease 2 (TMPRSS2) , both of which are pivotal membrane bound receptors
41 involved in host cell entry of severe acute respiratory syndrome coronavirus 2
42 (SARS-CoV-2)³. Moreover in patients with type 2 asthma exposure to exogenous
43 interleukin-13 in ex vivo primary airway epithelial cells decreases ACE2 and
44 increases TMPRSS2 expression⁴. Whether altered cell receptor expression might
45 translate into reduced viral load with ICS therapy is unknown .
46 There are also preliminary data to perhaps suggest a more specific salutary effect of
47 ICS with COVID-19 . In vitro experiments have shown that ICS may not all be same
48 in that low concentrations of ciclesonide and mometasone but not fluticasone
49 ,budesonide or beclomethasone appear to suppress replication of SARS-CoV-2 , to
50 the same degree as lopinavir .⁵ The inhibitory action of ciclesonide on replication of

51 SARS-CoV-2 was mediated via non-structural protein 15 (NSP15) . There have been
52 case reports of COVID-19 pneumonia successfully treated with inhaled ciclesonide
53 but no data yet from ongoing randomised controlled trials (NCT04416399,
54 NCT04381364, NCT04377711). In respect of COVID pneumonia inhaled ciclesonide
55 achieves high alveolar deposition and prolonged lung retention due to formation of
56 intracellular fatty acid conjugates, in addition to producing minimal systemic adverse
57 effects at higher doses .

58 As an initial step health informatics studies may help to elucidate if ICS might
59 alleviate or worsen COVID-19 outcomes in asthma patients, in particular looking at
60 dose response effects . Randomized controlled trials may also be warranted in patients
61 who do not have asthma perhaps to see if secondary prevention with ICS including
62 ciclesonide or mometasone can prevent progression of early COVID infection in
63 susceptible older patients with comorbidities . Meanwhile for patients with asthma the
64 current guidance is to continue taking their ICS containing controller therapy because
65 ultimately this may also confer optimal protection against viral infections including
66 SARS-CoV-2 and also prevent eosinophilic related exacerbations .

67 Figure Legend

68

69 Depicts putative positive and negative effects of inhaled corticosteroids in COVID-19
70 infection on (a) viral replication of severe acute respiratory syndrome coronavirus 2
71 (SARS-CoV-2) including specific effects of mometasone furoate and ciclesonide on
72 non structural protein 15 (NSP15), (b) reduced expression of angiotensin converting
73 enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) , (c) suppression
74 of pro-inflammatory cytokines including interleukin-6 (IL6) , (d) promotion of

- 75 secondary bacterial infection , (e) effects on neutrophils and eosinophils , (f)
- 76 suppression of adrenal secretion of cortisol and aldosterone

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