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Evidence - Budesonide Is Safe, Effective Early and Late Treatment for COVID-19

Richard Bartlett[1], Jon Fleetwood[2]*

[1]MD, Hospital Emergency Room Medical Director, Bartlett Emergency Group President, Texas HHS Meritorious Award Recipient, budesonideworks.com, USA.

[2]Founder & Editor-in-Chief, JonFleetwood.com, USA.

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Address for correspondence: Jon Fleetwood, Founder & Editor-in-Chief, JonFleetwood.com, USA.

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ABSTRACT

In the ongoing battle against COVID-19, identifying effective treatments remains critical. This paper examines the safety and efficacy of budesonide, an inhaled corticosteroid, as both an early and late-stage treatment for COVID-19. Drawing on a comprehensive review of global research, including the U.K. STOIC and PRINCIPLE trials, the Brazil TOGETHER trial, and additional studies from Saudi Arabia, Australia, and India, we provide robust evidence supporting budesonide's therapeutic potential. Notably, the U.K. Department of Health and the India Ministry of Health and Family Welfare have recommended budesonide for COVID-19 patients, underscoring its clinical relevance. Furthermore, budesonide's antiviral properties and its inclusion in the WHO's list of essential medicines highlight its importance in managing the pandemic. The paper also addresses regulatory implications, particularly concerning the FDA's Emergency Use Authorization (EUA) criteria, which consider budesonide as a viable alternative to experimental COVID-19 vaccines. Overall, our analysis advocates for the broader adoption of budesonide in COVID-19 treatment protocols, emphasizing its accessibility, affordability, and efficacy in reducing disease severity and improving patient outcomes.

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I. DR. BARTLETT'S PUBLISHED PROTOCOL IN GLOBALJOURNALS.ORG

A 2020 publication [1] in Global *Journal of Science Frontier Research* titled "SARS-Cov-2 and the Case for Empirical Treatment" written by Doctors Richard Bartlett and Alexandria Watkins represented an "outpatient case study that examines two patients in the United States with unique cases that involve oncology and Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV- 2), also known as COVID-19". The study "affirmed that an empirical treatment protocol with nebulized budesonide and the efficacy of treating symptomatic patients earlier rather than later has significant implications". The treatment plan even became "more effective by increasing the dosage and frequency of nebulized budesonide", according to the authors. A successful empirical treatment plan [2] included 0.5mg of nebulized budesonide "twice daily" and "clarithromycin (Biaxin) 500mg tab twice daily for ten days, Zinc 50mg tab twice daily, and aspirin 81mg tab daily". Bartlett's paper noted that there is a "decreased risk of pneumonia in COPD patients who use nebulized budesonide". "Secondary bacterial infection of the lung (pneumonia) was extremely common in patients with COVID-19", according to a report from Northwestern Medicine [3], citing data from an April 2023 study in *The Journal of Clinical Investigation* [4].

II. U.K. STOIC TRIAL

A July 2021 publication [5] in peer-reviewed medical journal *The* Lancet *Respiratory Medicine* "tested if inhaled glucocorticoids would be an effective treatment for early COVID-19". The study authors from Oxford University found that "early administration of inhaled budesonide reduced the likelihood of needing urgent medical care and reduced time to recovery after early COVID-19". The study represented an "open-label, parallel-group, phase 2, randomised controlled trial". It concluded that "inhaled budesonide, when given to adults with early COVID-19, reduced the likelihood of requiring urgent care, emergency department consultation, or hospitalisation". Budesonide administration allowed for "a quicker resolution of fever, a known poor prognostic marker in COVID-19". The authors also revealed that "self-reported and questionnaire-reported symptom resolution was faster". Moreover, there were "fewer participants with persistent COVID-19 symptoms at days 14 and 28 after budesonide therapy compared with usual care". The authors believe their study represents

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"the first interventional trial to study the efficacy of inhaled corticosteroids in early COVID-19 illness". This STOIC trial "potentially provides the first easily accessible effective intervention in early COVID-19", according to the researchers. "By assessing health-care resource use, the study provides an exciting option to help with the worldwide pressure on health-care systems due to the COVID-19 pandemic", they write. "Data from this study also suggest a potentially effective treatment to prevent the long-term morbidity from persistent COVID-19 symptoms".

A February 2021 University of Oxford publication [6] titled "Common asthma treatment reduces need for hospitalisation in COVID-19 patients, study suggests" confirmed that the Lancet's STOIC trial did find that early treatment with budesonide "appears to significantly reduce the need for urgent care and hospitalisation in people with COVID-19" and "reduced recovery time". Inhaled budesonide "reduced the relative risk of requiring urgent care or hospitalisation by 90% in the 28-day study period", Oxford states. Participants taking budesonide "also had a quicker resolution of fever, symptoms and fewer persistent symptoms after 28 days". Oxford referenced Professor Mona Bafadhel of the University's Nuffield Department of Medicine, who said she was "heartened that a relatively safe, widely available and well-studied medicine such as an inhaled steroid could have an impact on the pressures we are experiencing during the pandemic". Bafadhel, a Respiratory Consultant also working at the Oxford University Hospitals NHS Foundation Trust, commented on budesonide's ability to reduce persistent COVID symptoms, calling it "an important finding". "I am encouraged to see the reduction in persistent symptoms at 14 and 28 days after treatment with budesonide. Persistent symptoms after the initial COVID-19 illness have emerged as a long-term problem. Any intervention which could address this would be a major step forward", she stated.

III. U.K. PRINCIPLE TRIAL

An August 2021 publication [7] in *The Lancet* titled "Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial", based on Oxford University's [8] 'Platform Randomised Trial of Interventions against COVID-19 in Older People' aimed to "establish whether inhaled budesonide reduces time to recovery and COVID-19-related hospital admissions or deaths among people at high risk of complications in the community". This PRINCIPLE test represented a "multicentre, open-label, multi-arm, randomised, controlled, adaptive platform trial done remotely from a central trial site and at primary care centres in the UK", according to the authors. Budesonide conferred "a benefit in time to first self-reported recovery" and lessened "hospital admission or death outcome". The authors conclude, "Inhaled budesonide improves time to recovery, with a chance of also reducing hospital admissions or deaths … in people with COVID-19 in the community who are at higher risk of complications". While the authors noted that results pertaining to hospitalization and death "did not meet the superiority threshold", they clarified that "this might have been due to the rapid decrease in rate of hospital admissions or deaths in March and April, 2021, in the UK, because of the vaccination programme and lockdown measures". They went on to emphasize, "Overall, the consistency of these findings across both primary and secondary endpoints provides the strongest evidence thus far of an effective, safe, cheap, and readily available treatment for COVID-19 in the community". This PRINCIPLE trial "is the largest randomised trial thus far to assess inhaled budesonide for community treatment of COVID-19". It confirmed that "inhaled budesonide reduced COVID-19-related emergency assessments or hospital admissions, compared with usual care, and self-reported recovery favoured budesonide by 1 day". The study authors

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also affirmed that "several randomised trials have shown that systemic corticosteroids reduce mortality among people admitted to hospital with COVID-19, with the RECOVERY trial finding greatest benefit in mechanically ventilated patients". The PRINCIPLE trial "has provided evidence of a safe and cheap community treatment for COVID-19 that reduces symptom burden and enhances sustained recovery over 28 days, with a high probability of also reducing the need for hospital admission". Inhaled budesonide "is available in many primary care settings and is included in the WHO list of essential medicines", the authors highlighted (SEE VI). "Our study provides evidence that inhaled budesonide is an effective and safe treatment for people with COVID-19 in the community who are at increased risk of adverse outcomes".

An August 2021 commentary published [9] in Annals *of Medicine & Surgery* titled "Budesonide: A promising candidate therapeutic for early COVID-19" cited the above Lancet study, noting its "promising results of budesonide in treating patients with mild COVID-19 infection". The authors underscored how "patients taking inhaled budesonide had a faster COVID-19 recovery time by 3 days than patients who received only usual care along with lower hospitalizations in the budesonide group than the usual care group". They referenced the U.K. government's conclusion that budesonide "can be considered (off label) on a case-by-case basis for symptomatic covid-19 positive patients aged 65 and over, or aged 50 or over with co-morbidities" (SEE VII). The authors state budesonide is a "a potent topical anti-inflammatory agent" in that it effectively translocates into the cell nucleus, prevents the expression of pro-inflammatory genes, increases the expression of anti-inflammatory genes, and "inhibits the eosinophil activation by increasing apoptosis and suppresses the activation of various inflammatory cells such as neutrophils, mast cells, macrophages, T-lymphocytes, and dendritic cells". Budesonide administration therefore "leads to reduced airway inflammation and hyperreactivity resulting into inhibition of the bronchospasm and subsequently wheezing and coughing", according to the authors. They conclude that inhaled budesonide "is a simple, safe, very well studied, widely available, and inexpensive corticosteroid which may prove crucial for mild COVID-19 cases". Budesonide "could give healthcare workers more options in treating COVID-19 patients, especially as it is readily available in most of the primary healthcare settings and is listed as Essential Medicine in the World Health Organization's List of Essential Medicines", they conclude, and "can be used with ease even in comorbid, unwell, and potentially frail older patients".

An April 2021 publication [10] in *The British Medical Journal* (BMJ) titled "Covid-19: Budesonide shortens recovery time in patients not admitted to hospital, study finds" also recognized Oxford's findings published in the Lancet, affirming that budesonide "can shorten the time it takes for people not admitted to hospital to recover from covid-19 by three days". The BMJ piece emphasized how those treated with budesonide "also reported greater wellbeing after two weeks". Less of those treated with budesonide "were admitted to hospital" than those who did not. The author for BMJ cited Fiona Watt, Executive Chair of the Medical Research Council, who said that "researchers involved in the Principle trial have overcome considerable logistical hurdles to set up a world leading rigorous drug trial in people's homes". Watt added, "We are now rewarded with the first inexpensive and widely available drug that can shorten recovery times for covid-19 patients in the community". The author also cited Joint Chief Investigator Chris Butler, a south Wales GP and Professor of Primary Care from the University of Oxford, who said, "We therefore anticipate that medical practitioners around the world caring for people with covid-19 in the community may wish to consider this evidence when making treatment decisions".

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The Lancet PRINCIPLE study authors published [11] "Inhaled Budesonide for COVID-19 in People at Higher Risk of Complications in the Community: The UK National Community Randomi" in *Annals of Family Medicine* in January 2023. In that publication, they confirm that inhaled budesonide (800µg twice daily for 14 days) led to "shorter" time to first self-reported recovery compared to usual care and less hospitalizations and deaths compared to usual care.

IV. BRAZIL TOGETHER TRIAL

A May 2023 publication [12] in *Annals of Internal Medicine* titled "Oral Fluvoxamine with Inhaled Budesonide for Treatment of Early-Onset COVID-19" set out to "determine whether the combination of fluvoxamine and inhaled budesonide would increase treatment effects in a highly vaccinated population" in a randomized, placebo-controlled, adaptive platform trial. "Patients were randomly assigned to either fluvoxamine (100 mg twice daily for 10 days) plus inhaled budesonide (800 mcg twice daily for 10 days) or matching placebos", the study reads. The number of patients "observed in an emergency setting for COVID-19 for more than 6 hours or hospitalized due to COVID-19 was lower in the treatment group than the placebo group". The authors conclude that treatment with oral fluvoxamine plus inhaled budesonide "among high-risk outpatients with early COVID-19 reduced the incidence of severe disease requiring advanced care". The study was "among the first to evaluate a drug combination for treatment of ambulatory patients with COVID-19 in a randomized trial", according to the authors. They "found a reduction in the composite end point for COVID-19 disease progression with a combination of oral fluvoxamine, 100 mg twice daily, and inhaled budesonide". Budesonide and fluvoxamine "reduced the need for advanced medical care". Moreover, the "number of serious adverse events associated with this combination therapy was lower than in the placebo group". The authors confirm that "In conclusion, administration of the combination of fluvoxamine, 100 mg twice daily, and inhaled budesonide reduced the rate of COVID-19 progression resulting in prolonged observation in an emergency setting or hospitalization among outpatients with high risk for serious disease".

V. SAUDI JOURNAL OF ANESTHESIA STUDY

A January 2017 publication [13] in *Saudi Journal of Anesthesia* "tested the hypothesis that nebulized budesonide would improve lung mechanics and oxygenation in patients with early acute lung injury (ALI) and/or acute respiratory distress syndrome (ARDS) during protective mechanical ventilation strategy without adversely affecting systemic hemodynamics". Patients received "1 mg–2 ml budesonide suspension … nebulized through the endotracheal tube" every "12 h for three successive days alongside with constant ventilator settings". The study authors found that nebulized budesonide "improved oxygenation, peak, and plateau airway pressures and significantly reduced inflammatory markers (TNF-α, IL-1β and IL-6) without affecting hemodynamics". Budesonide "inhibits a variety of inflammatory cells, reduces the production of inflammatory mediators and consequently has a significant anti-inflammatory effect". It "induces vasoconstriction, inhibits mucosal edema, reduces cell exudation, and prevents airway remodeling". It can "obtund the sequelae of the acute phase response and reduces alveolar inflammation". Budesonide "inhibits airway inflammation, alleviates edema, inhibits remodeling and promotes suctioning which maintains pulmonary function during mechanical ventilation". It "reduces the adverse events associated with systemic corticosteroid administration such as increased blood glucose level, hypothalamic-pituitary-adrenal axis suppression, bone demineralization, perforated peptic ulcer, and altered immunity". Budesonide "can act as a pulmonary protective agent during

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mechanical ventilation for ALI/ARDS patients". Late COVID results in ARDS, this study proving that budesonide is an effective and safe treatment for ARDS.

VI. WHO LISTS BUDESONIDE AS ESSENTIAL MEDICINE

A July 2019 World Health Organization (WHO) publication [14] titled "WHO model list of essential medicines - 21st list, 2019" recommends budesonide inhaled (aerosol) at "100 micrograms per dose" and "200 micrograms per dose" as one of its "medicines acting on the respiratory tract".

VII. U.K. DEPARTMENT OF HEALTH RECOMMENDS BUDESONIDE FOR ADULTS 50 OR OVER

An April 2021 U.K. Department of Health alert [15] from Chief Medical Officer Dr. Michael McBride titled "COVID-19 THERAPEUTIC ALERT - INHALED BUDESONIDE FOR ADULTS (50 YEARS AND OVER) WITH COVID-19" stated that inhaled budesonide "can be considered (off-label) on a case-by-case basis for symptomatic COVID-19 positive patients aged 65 and over, or aged 50 or over with co-morbidities, in line with the published Interim Position Statement".

The aforementioned April 2021 BMJ publication (SEE III) recognized the U.K. government health alert affirming that budesonide "can be considered" to treat COVID-19.

VIII. AUSTRALIA RECOMMENDS BUDESONIDE FOR ADULTS WITH COVID-19

Australia's Department of Health, through its National Clinical Evidence Taskforce, published [16] a document titled "COVID-19 medications for at risk people who do not require oxygen" in June 2022 that recommends budesonide at "800 µg inhaled twice daily for up to 14 days". Budesonide "can be considered as either a standalone therapy or as an additional therapy in patients already prescribed another early therapy", according to the document.

IX. INDIA MINISTRY OF HEALTH AND FAMILY WELFARE RECOMMENDS BUDESONIDE FOR ADULTS WITH COVID-19

India's Ministry of Health and Family Welfare published [17] a document titled "Clinical Management Protocol for COVID-19" in May 2021 that recommends budesonide "given via inhalers with spacer at a dose of 800 mcg twice daily for 5 to 7 days".

X. ANTIVIRAL EFFECT OF BUDESONIDE AGAINST COVID-19

A July 2021 publication [18] in *Viruses* titled "Antiviral Effect of Budesonide against SARS-CoV-2" analyzed the "potential antiviral activity of budesonide" and potentially indicates a "multimodal mode of action of budesonide against SARS-CoV-2 and COVID-19". The study results "suggest that treatment with budesonide reduces titers of SARS-CoV-2 and VOCs significantly while cell viability remains unaffected", according to the authors. They "observed significant reduction of viral titers for all viral variants in vitro when cells were treated with 25 µM budesonide".

XI. FDA RULES PROHIBIT AGENCY FROM GRANTING EMERGENCY USE AUTHORIZATION (EUA) FOR EXPERIMENTAL COVID-19 VACCINES BECAUSE BUDESONIDE WORKS

The U.S. Food & Drug Administration (FDA) affirms that it "can use its Emergency Use Authorization (EUA) authority under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to allow the use of unapproved medical products, or

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unapproved uses of approved medical products, to diagnose, treat, or prevent serious or life-threatening diseases when certain criteria are met", according to the FDA website [19]. This is "including that there are no adequate, approved, and available alternatives". Section 564 states that an EUA can only be granted if "there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating such disease or condition" [20]. But Budesonide is an "adequate, approved [21], and available alternative" to COVID-19 vaccines, thus meeting the FDA's section 564 criteria prohibiting the EUA of COVID vaccines. Therefore, experimental COVID vaccines EUAs are void and illegal. Present and future production of COVID vaccines and/or gene therapies must cease and desist. The FDA is currently egregiously violating its own rules.

CONCLUSION

Inhaled budesonide represents a safe, effective, and readily available treatment for COVID-19, particularly when administered early. Its ability to reduce the need for urgent medical care and expedite recovery offers a valuable tool in the ongoing fight against the pandemic. Furthermore, evidence suggests that budesonide is also effective in the late stages of COVID-19, helping to mitigate severe symptoms and improve patient outcomes. Budesonide has been shown via Randomized Controlled Studies to benefit patients with Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS), which are sequelae of late COVID-19 disease. Regulatory bodies and healthcare providers should incorporate budesonide into treatment protocols based on its safety profile and clinical benefits. Continued research will further elucidate its role and optimize its use in diverse patient populations.

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