Ventilating my thoughts on severe asthma exacerbations

In this issue of *AJTCCM*, Manyeruke *et al.*[1] provide a retrospective review of 110 acute asthma exacerbations requiring mechanical ventilation (103 patients) in the respiratory intensive care unit (ICU) at Groote Schuur Hospital, Cape Town, South Africa (SA), over a 6-year period (2014 - 2019). Theoretically, all hospital admissions for asthma represent failure of one or more aspects of management of this common chronic disease – timely and correct diagnosis, avoidance of precipitating factors, smoking cessation, appropriate drug therapy, proper inhaler use technique, adherence to therapy, patient education, and regular review.

The striking findings were: (*i*) only 60.0% of the patients were using inhaled corticosteroids (ICSs), although 91.8% were using short-acting beta-agonists (SABAs); (*ii*) the median partial pressure of carbon dioxide ($PaCO_2$) on admission to the ICU was 9.09 kPa (68.2 mmHg); (*iii*) the median pH was 7.22; (*iv*) 7 patients (6.4%) had had a previous ICU admission; (*v*) 10.9% were using long-term oral corticosteroids (OCSs); (*vi*) 36.4% were current smokers; and (*vii*) 14.5% admitted to illicit drug abuse.

Current practice mandates ICSs as the mainstay of asthma drug therapy, since these drugs address the underlying pathogenesis of airway inflammation. ICS use in asthma has been shown to control symptoms, decrease exacerbations and hospitalisations, and even reduce mortality.[2] In 2019, the Global Initiative for Asthma (GINA) instituted a paradigm change by advocating that SABA monotherapy should never be prescribed in the treatment of asthma, even in mild disease, as this was associated with an increased risk of exacerbations and asthma-related mortality.[3]

While there is incontrovertible evidence for the value of ICSs, these drugs demonstrate flat dose-response curves for their beneficial clinical effects, with 80 - 90% of the maximum benefit obtained with 'low-dose' ICSs (fluticasone propionate 100 - 250 µg daily or equivalent).[4] In contrast, the higher the dose of ICSs, the greater are the systemic side-effects, a phenomenon that does not plateau. Notably, a large real-world study employing two electronic UK medical record databases showed that increasing the dose of ICSs in poorly controlled asthmatics to dosages considered 'high dose' was associated with a higher risk of exacerbations and a reduced time to first exacerbation.[5] We also now recognise that the magnitude of response to corticosteroids varies between different asthma phenotypes and endotypes.[6]

Even in patients co-prescribed an ICS, SABA overuse (>2 standard canisters per year) is coupled with increased asthma exacerbations and poorer asthma control. A positive relationship between the number of SABA canisters prescribed per patient per year and these unfavourable outcomes was evident in the SABINA studies.[7,8] It is sobering to note that of 24 countries across four continents surveyed in the SABINA III study, SA fared worst, with 74.9% of mild or moderate-to-severe asthmatics prescribed ≥3 SABA canisters per year and 56.5% prescribed ≥10 canisters per year.[7]

How do the features and outcomes of this SA study compare with the developed world? A large study of patients with asthma admitted to ICUs from 2014 - 2015 that compared Australian and New Zealand (ANZ) patients with those in the USA was reported by Abdelkarim *et al.*[9] Seven hundred and thirty patients were intubated (ANZ *n*=544, USA *n*=186). Comparing the intubated patients in the ANZ cohort with those in the US cohort, the median age was 45 and 41 years, respectively, most were female (62.3% and 64.0%), the median $PaCO_2$ was 54 and 46 mmHg, the median pH was identical (7.35), ICU length of stay (LoS) was 3.1 and 2.5 days, and ICU mortality was 2.0% and 5.4%. Manyeruke *et al.*'s patients were much younger (median age 33.5 years) and had more severe hypercapnia and acidosis. Despite the more severely deranged blood gas parameters, suggesting delayed presentation and/or greater severity of exacerbations, the ICU LoS was similar (median 3 days) and the ICU mortality comparable (4.5%). There was also a female predominance (53.6%).

Asthma patients are not immune to tobacco addiction. In a nationally representative telephonic survey of 12 339 asthmatics in the USA (21.8% of whom were current smokers) who had visited the emergency department (ED) over the past year,[10] the odds of current smokers having visited the ED was 1.82 compared with never smokers. In another study, 35% of 1 847 patients who presented to the ED with acute asthma were current smokers (median 10 pack-years).[11] Interestingly, only 4% of these subjects considered this acute episode to be related to their smoking habit, although 50% acknowledged that cigarette smoke was a triggering factor for their asthma.

Asthmatics who are also cannabis users are known to have poorer asthma control and more frequent exacerbations. This association is complex, as many are also tobacco users, have poor socioeconomic circumstances and are poorly adherent to treatment. In a case-control observational study, 44% of asthmatics who presented to the ED with an acute exacerbation either admitted to use of illicit drugs or had a positive urine test for illicit drugs.[12] Smoked cannabis has been shown to cause bronchodilation lasting ~60 minutes,[13] probably mediated via CB1 receptor stimulation in airway parasympathetic nerves that leads to inhibition of acetylcholine release. Despite isolated reports of cannabis improving asthma control,[14] a Norwegian study based on asthma prescriptions suggests that current cannabis smoking may be a risk factor for asthma.[15] A laboratory-based study suggests that smoking cannabis decreases the conversion of beclomethasone dipropionate (BDP) to its active metabolite, beclomethasone-17-monopropionate.[16] The clinical significance of possible interactions between inhaled cannabis and BDP or other ICSs has not been studied. Cannabis has been reported to cause allergic manifestations,[17,18] including asthma, allergic rhinitis, eczema and even anaphylaxis. Sensitivity may be related to exposure to pollen or seeds of the *Cannabis sativa* plant, recreational use or occupational exposure.

In Manyeruke *et al.*'s study, 10.9% of the patients were using chronic OCSs. The mean daily dose was not stated. Low-dose systemic steroids (prednisone ≤7.5 mg/d) is an option in step 5 of the GINA guideline, but only 'as a last resort'.[19] In a systematic review of the use of systemic corticosteroids prescribed for asthma,[20] long-term corticosteroid use ranged from 1.2% to 30.9% in patients with any degree of asthma severity. Long-term OCS use was associated with a 3.6-fold increase in steroid-related side-effects compared with no use. The risks of adverse effects are related to the cumulative dose, so even patients prescribed frequent courses of short-term OCSs are predisposed to these unintended consequences.

Of concern is that only 61.5% of survivors in Manyeruke *et al.*'s study returned for a follow-up visit to the respiratory clinic at Groote Schuur Hospital. A history of substance abuse was a significant risk factor for defaulting.

The World Asthma Day 2023 theme for 2 May was 'Asthma care for all'. SA remains far from addressing asthma, one of the most common chronic respiratory diseases, in an adequate manner. Despite having world experts in asthma and comprehensive national asthma guidelines in our country, translation at grassroots level remains woefully poor. Cape Town is a thriving metropolis with arguably the best primary healthcare infrastructure in the country, yet the statistics for severe asthma exacerbations do not reflect this. Like most chronic diseases, diagnosis and management of asthma extend beyond scientifically based guidelines. Important aspects beyond our control include political commitment and support, improved access to healthcare and emergency services, availability and cost of drugs, transport, socioeconomic deprivation, pollution control, and tobacco and illicit drug use.

Things we can do to improve the situation are education (of the lay public, patients with asthma, medical students, primary healthcare providers, general practitioners, specialists), ensuring that all asthmatics are prescribed an ICS, advocacy for drugs and newer formulations to be available and at lower cost (including biological agents), checking inhaler technique at every visit, promotion of smoking cessation, regular follow-up, and earlier interventions in acute exacerbations. We have a lot of work to do.

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1. Manyeruke F, Calligaro GL, Raine R, van Zyl Smit RN. Asthma in the intensive care unit: A review of patient characteristics and outcomes. Afr J Thoracic Crit Care Med 2023;29(2):e212. https://doi.org/10.7196/AJTCCM.2023.v29i2.212
2. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med 2000;343(5):332-336. https://doi.org/10.1056/NEJM200008033430504
3. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf (accessed 3 May 2023).
4. Beasley R, Harper J, Bird G, Maijers I, Weatherall M, Pavord ID. Inhaled corticosteroid therapy in adult asthma: Time for a new therapeutic dose terminology. Am J Respir Crit Care Med 2019;199(12):1471-1477. https://doi.org/10.1164/rccm.201810-1868CI
5. Pavord ID, Tran TN, Jones RC, et al. Effect of stepping up to high-dose inhaled corticosteroids in patients with asthma: UK Database Study. J Allergy Clin Immunol Pract 2023;11(2):532-543. https://doi.org/10.1016/j.jaip.2022.10.040
6. Kuruvilla ME, Lee FE, Lee GB. Understanding asthma phenotypes, endotypes, and mechanisms of disease. Clin Rev Allergy Immunol 2019;56(2):219-233. https://doi.org/10.1007/s12016-018-8712-1
7. Bateman ED, Price DB, Wang HC, et al. Short-acting beta(2)-agonist prescriptions are associated with poor clinical outcomes of asthma: The multi-country, cross-sectional SABINA III study. Eur Respir J 2022;59(5):2101402. https://doi.org/10.1183/13993003.01402-2021
8. Khattab A, Madkour A, Ambaram A, et al. Over-prescription of short-acting beta(2)-agonists is associated with poor asthma outcomes: Results from the African cohort of the SABINA III study. Curr Med Res Opin 2022;38(11):1983-1995. https://doi.org/10.1080/03007995.2022.2100649
9. Abdelkarim H, Durie M, Bellomo R, et al. A comparison of characteristics and outcomes of patients admitted to the ICU with asthma in Australia and New Zealand and United States. J Asthma 2020;57(4):398-404. https://doi.org/10.1080/02770903.2019.1571082
10. Khokhawalla SA, Rosenthal SR, Pearlman DN, Triche EW. Cigarette smoking and emergency care utilization among asthmatic adults in the 2011 Asthma Call-back Survey. J Asthma 2015;52(7):732-739. https://doi.org/10.3109/02770903.2015.1004337
11. Silverman RA, Boudreaux ED, Woodruff PG, Clark S, Camargo CA Jr. Cigarette smoking among asthmatic adults presenting to 64 emergency departments. Chest 2003;123(5):1472-1479. https://doi.org/10.1378/chest.123.5.1472
12. Gaeta TJ, Hammock R, Spevack TA, Brown H, Rhoden K. Association between substance abuse and acute exacerbation of bronchial asthma. Acad Emerg Med 1996;3(12):1170-1172. https://doi.org/10.1111/j.1553-2712.1996.tb03386.x
13. Tashkin DP, Shapiro BJ, Frank IM. Acute pulmonary physiologic effects of smoked marijuana and oral (delta)9-tetrahydrocannabinol in healthy young men. N Engl J Med 1973;289(7):336-341.
14. Jarjou'i A, Izbicki G. Medical cannabis in asthmatic patients. Isr Med Assoc J 2020;22(4):232-235.
15. Bramness JG, von Soest T. A longitudinal study of cannabis use increasing the use of asthma medication in young Norwegian adults. BMC Pulm Med 2019;19(1):52. https://doi.org/10.1186/s12890-019-0814-x
16. Qian Y, Melchert PW, Markowitz JS. Involvement of esterases in the pulmonary metabolism of beclomethasone dipropionate and the potential influence of cannabis use. Chem Biol Interact 2022;368:110228. https://doi.org/10.1016/j.cbi.2022.110228
17. Ocampo TL, Rans TS. *Cannabis sativa*: The unconventional 'weed' allergen. Ann Allergy Asthma Immunol 2015;114(3):187-192. https://doi.org/10.1016/j.anai.2015.01.004
18. Chatkin JM, Zani-Silva L, Ferreira I, Zamel N. Cannabis-associated asthma and allergies. Clin Rev Allergy Immunol 2019;56(2):196-206. https://doi.org/10.1007/s12016-017-8644-1
19. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2023. Updated May 2023. https://ginasthma.org/wp-content/uploads/2023/05/GINA-2023-Full-Report-2023-WMS.pdf (accessed 9 May 2023).
20. Bleecker ER, Menzies-Gow AN, Price DB, et al. Systematic literature review of systemic corticosteroid use for asthma management. Am J Respir Crit Care Med 2020;201(3):276-293. https://doi.org/10.1164/rccm.201904-0903SO

Afr J Thoracic Crit Care Med 2023;29(2):e1229. https://doi.org/10.7196/AJTCCM.2023.v29i2.1229