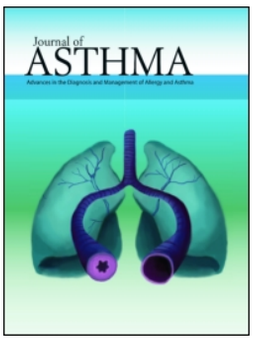

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COMMENTARY

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Position statement: asthma in Latin America. IS short-acting beta-2 agonist helping or compromising asthma management?

L. J. Nannini, MD[a], S. Luhning, MD[b], R. A. Rojas, MD[c], J. M. Antunez, MD[d], J. L. Miguel Reyes, MD[e], C. Cano Salas, MD[e], and R. Stelmach, MD[f]

[a]Hospital de G. Baigorria, Universidad Nacional Rosario, Santa Fe, Argentina; [b]Hospital Nacional de Clínicas, Córdoba, Argentina; [c]Instituto Investigaciones de Patologías Respiratorias, San Miguel de Tucumán, Argentina; [d]Clínica Alemana, Vitacura, Chile; [e]Instituto Nacional de Enfermedades Respiratorias, Ciudad de México, Mexico; [f]Pulmonary Division –Heart Institute (InCor), Hospital das Clinicas, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

ABSTRACT

In Latin-America, with 603 million inhabitants, the average prevalence of asthma is estimated at 17%, but with wide fluctuations, ranging from 5% in some cities (Mexico) to 30% in Costa Rica. The risk of severe exacerbations seems to be higher in Latin America compared with other regions. A majority of patients uses daily quick-relief medication, with the belief that it is the most important treatment because of its rapid onset of action; without treating the underlying inflammation. Overuse of short-acting beta$_2$ agonists (SABAs) is associated with increased risk of asthma deaths in a dose–response manner. Beta$_2$ agonists increase the severity of asthma through enhanced bronchial hyperresponsiveness and reduced lung function. Also, it has been shown that overreliance on SABA delays recognition of a potentially life-threatening asthma attack. We believe that overreliance on SABA in asthma is also an important public health issue. The fact that SABA use in GINA is not supported by a randomized trial but by an anonymous paper; makes us guess that we use SABA just because we are used to do so. In 2019 GINA strategy introduces one of the most important changes in the management of Asthma in the past 30 years, highlighting anti-inflammatory reliever therapy. A combination of low dose ICS/fast action bronchodilator will not only treat symptoms, but more importantly the underlying inflammation, protecting patients from preventable asthma attacks. After 50 years of a SABA centric approach in asthma management, it is time to leave behind a treatment based just on the bronchodilation and tackle the inflammation.

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Brief epidemiological aspects of asthma in Latin America

Latin-America is a geographically, politically, and economically diverse region comprising 20 countries whose languages are primarily Spanish and Portuguese. Regional variation in the prevalence of asthma is likely multifactorial and due to genetics, perinatal exposures, diet, obesity, tobacco use, in- and outdoor pollutants, psychosocial stress and microbial or parasitic infections (1). Similarly, non-uniform progress in asthma management leads to regional variability in disease morbidity. Some problems may be unique to specific countries, but some of them share similar barriers to asthma management, thus concerted public health and research efforts are needed.

Despite the difficulties in diagnosis and the different regional realities, asthma is a frequently occurring disease that affects $\geq$ 339 million people around the world (2). The global prevalence varies from 6.1% to 24%. In Latin-America, with 603 million inhabitants, the average prevalence of asthma is estimated at 17%, but with wide fluctuations, ranging from 5% in some cities in Mexico to 30% in Costa Rica (3).

In relation to severity, some research indicates that asthma in Latin-America is predominantly mild to moderate, but up to 20% of patients could have severe asthma, with a strong impact at a regional level.

CONTACT L. J. Nannini ljnannini@hotmail.com Hospital de G. Baigorria, Universidad Nacional Rosario, San Martin 1651, Hospital E Peron de G Baigorria, Santa Fe 2000, Argentina.

AstraZeneca LATAM provided the sources for a meeting during the ALAT Congress 2019 at Panama.

Most of patients ($\geq$ 60%) uses quick-relief medication daily, with the belief that it is the most important treatment because of its rapid onset of action, contrary to guideline recommendations (4,5). These results reveal an ongoing need for the improvement in asthma care and education in most populations. Although there has been a marked and progressive reduction in international asthma mortality since the late 1980s, no appreciable change in global asthma mortality in 5 to 34-year olds could be shown since 2006 (6). Recognizing the fact that about half of asthma deaths are preventable, if recommended guidelines were followed, a better implementation of established management strategies is needed. However, to achieve a further substantive reduction in asthma mortality, novel strategies are required.

Over-reliance on short-acting bronchodilators is linked to poor outcomes in patients with asthma

The overuse of short-acting beta$_2$ agonists (SABAs) is associated with the increased risk of asthma deaths in a dose–response manner (7). SABAs (egsalbutamol, terbutaline, and fenoterol) became key agents patients with asthma because of temporary control of symptoms and rapid onset of action but failed to treat the underlying pathology, namely airway inflammation; in fact, SABA promotes more inflammation and bronchial hyperresponsiveness (8,9). The over-reliance on SABA could be the cause of the sustained mortality from asthma in the past decade and the poor adherence to the controller anti-inflammatory treatment (10). In addition, in Latin America some Health Authorities approved oral SABA monotherapy for the prevention of bronchoconstriction caused by asthma (11).

It is well recognized that SABA as a drug class have the potential for long-term adverse effects, increasing the severity of asthma through enhanced bronchial hyperresponsiveness and reduced lung function (12,13). Also, it has been shown that over-reliance on SABA delays a recognition of a potentially life-threatening asthma attack (13). Which circumstances are behind all of this? (1) SABA is the first pharmacological agent that is prescribed to almost all patients; (2) SABA does not have anti-inflammatory effects; (3) Individuals with Asthma tend to take more SABA when their symptoms worsen at the expense of true controller asthma treatments; (4) Mild patient adherence to ICS is low because it does not perceive an immediate beneficial effect as with SABA; (5) finally, SABA monotherapy should not be considered as a treatment for chronic asthma (10).

Is mild asthma really "mild"?

Approximately 50–75% of patients have mild asthma and of these, 30–40% may be at risk of severe exacerbations (14), requiring an emergency department visit (7) or leading to death (10) and an association with the overuse of SABA has been established (12). A combination of a fast-acting β2-agonist and ICS taken only 'as needed' for rapid symptom relief may address the underuse of ICS and reduce exacerbations for patients with mild asthma.

The SYGMA 1 & 2, Novel START and PRACTICAL studies (15–18) involve mild asthma patients receiving either SABA as needed, low dose budesonide/formoterol as needed or maintenance ICS ± SABA as needed and have demonstrated the benefits of starting ICS-containing medication in the early stages of the disease. A demographic and baseline characteristic post-hoc evaluation of a Latin-American population with mild asthma was performed in the SYGMA 1 and 2 studies (15,16), focusing on severe exacerbation rates in the past 12 months before inclusion in the studies.

Of 2447 Latin-American patients enrolled in the studies, a total of 1418 patients were randomized and 1366 patients were included in the full analysis and safety datasets ($n = 773$ in SYGMA 1 and $n = 633$ in SYGMA 2). We observed that 27.9% and 39.3% of the Latin-American population had at least one severe exacerbation during the 12 months before inclusion in the SYGMA 1 and 2 studies, respectively. Data for the overall study population showed that 19.7% and 22%, had at least one severe exacerbation during the 12 months before inclusion in SYGMA 1 and SYGMA 2, respectively. Therefore, all patients with asthma are at risk of severe exacerbations, independently of asthma severity. The risk of severe exacerbations seems to be higher in Latin America compared with other regions. This scenario could be related to higher social-economic and health structures diversity, inside and among countries, including access to specialists, examinations and, most importantly, to continuous affordable medicines.

If a patient with asthma is controlled with ICS/formoterol at step 3 of GINA recommendations, this new strategy would simplify a step-down approach in medical practice and avoids a fruitless discussion of trying to prescribe ICS alone treatment daily, leading to a lack of adherence in patients with infrequent symptoms. SABA as a reliever is always used as a disease control thermometer but will not prevent a future exacerbation. Low dose ICS-formoterol anti-inflammatory reliever is not only a disease alert but also the solution at the same time.

Over-prescription of SABA may be related to guidelines that emphasize symptom management

rather than the treatment of the inflammatory process. However, the 2017 Lancet Commission on asthma, indicate that first-line treatment should always include an anti-inflammatory medication (such as ICS), regardless of severity of asthma, instead of the current purely symptom-management with a bronchodilator.

GINA 2019 highlights

GINA has been developed as an evidence based comprehensive strategy, to provide recommendations for clinical practice, in order to improve asthma management (19).

Since 2007 and after many years of seeking a better intervention for mild asthma, the new recommendations of GINA 2019 propose a major change in Steps 1 and 2, tackling paradoxical messages from the past and incorporating new evidence. Thus, the report of the 2019 GINA strategy introduces one of the most important changes in the management of asthma in the past 30 years, highlighting the importance of mild asthma management, and recognizing the exacerbation risk, underestimated for so long.

Now, for safety reasons, GINA no longer recommends the use of SABA alone in step 1. Two strong arguments justify SABA withdrawal at this level: (1) the lack of scientific evidence that could support such recommendation in contrast with the strong evidence of safety, efficacy, and effectiveness of the ICS recommended for stages 2 to 5, (2) use of SABA only gives transient relief of symptoms without protection from severe exacerbations and hospitalizations and, also worsens asthma control with frequent and/or regular use.

As the use of SABA by GINA is not supported by a randomized trial but by an anonymous paper (20), this suggests we are using SABA reflexively thus perpetuating this asthma paradox (21). On the other hand, the recent studies provided the evidence that led to the major change in asthma management (15–18). Thus, replacing SABAs with an anti-inflammatory reliever is a new paradigm that is justified based on the inflammatory nature of asthma.

Discussion: Next steps

Overreliance on SABA is a multifactorial public health issue, related to patients, physicians, pharmacists, and decision makers. Addressing this topic poses great challenges: identifying the cause of overuse of SABA (knowledge, expectations, cultural aspects and beliefs, and very low cost of the drug) is complex, as is the identification of all actors involved (prescribers, dispensers, patients and community members). To tackle this issue, a multistep approach is needed, addressing all relevant stakeholders.

In 2018, the Pan American Health Organization (PAHO) published a comprehensive guidance on how to tackle the resistance to antibiotics in Latin America (22). It was recognized that up to 50% of the use of antibiotics was inappropriate, leading to increasing bacterial resistance and patients' morbidity and mortality and adding considerable costs to patient care.

Some specific points were identified and tackled: antibiotic self-medication, with recommendation of enforcement just with prescription, antibiotics stewardship concept to ensure appropriate use and setting educational standards for health care professionals, to address inappropriate prescription (non-adherence to standard treatment guidelines). Antibiotic prescription to viral infections could be an analogy of prescribing SABAs to asthma.

We believe that overreliance on SABA in asthma is also an important public health issue that should be addressed in a similar way like antibiotics have been addressed recently by the PAHO. Some initiatives already started in our region, including SABA-free institutions in Argentina, but a more comprehensive approach is now imperative, including regulatory framework and, patients', physicians' and pharmacists' education, among other measures. We should include low dose ICS in mild asthma every time patients require reliever medication with beta-agonists.

A combination of low dose ICS/fast action bronchodilator will not only treat symptoms, but also the underlying inflammation, protecting patients from preventable asthma attacks. After 50 years of a SABA centric approach in asthma management, it is time to leave behind a treatment based just on the bronchodilation and tackle the inflammation.

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Declaration of interest

LJN: personal fees as speaker for AstraZeneca and for Advisory boards from AstraZeneca and Sanofi-Genzime Argentina outside the submitted document. SL: personals fees from Astrazeneca outside the submitted work. RAR: personal fees from GlaxoSmithKline and AstraZeneca Argentina. MA: payment for services to AstraZeneca and Teva outside the submitted work. JLM: personals fees from Astrazeneca, GlaxoSmithKline, Boehringer Ingelheim and Novartis outside the submitted work. CC: personals fees

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ORCID

L. J. Nannini http://orcid.org/0000-0002-9868-9883
J. M. Antunez http://orcid.org/0000-0002-5759-0377
J. L. Miguel Reyes http://orcid.org/0000-0002-4071-3254
R. Stelmach http://orcid.org/0000-0002-5132-1934

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