

# On the Evidence that Augmentation Therapy Helps Asthma: Are Storks Really Responsible for New Babies?

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The case report by Blanco *et al.* in this issue of the journal [1] presents a young woman with PI\*MZ alpha-1 antitrypsin deficiency and asthma who was treated with intravenous augmentation therapy with apparent stabilization of her asthma following this therapy. This case report, the first of its kind (to my knowledge) to examine the impact of augmentation therapy for asthma and the first to report using augmentation therapy for a PI\*MZ individual, is both intriguing for the novelty of the observation and for its potential implications and, at the same time, challenging and troubling for the possibility that the uncritical reader could infer causality (i.e., that augmentation therapy somehow conferred the benefit) from the reported temporal correlation with improved asthma control in the single reported patient.

Indeed, the pitfalls of making causal inferences from observational data, even if from large data sets, are well known and have been amply discussed [2-4]. Classic objects of misinterpretation include studies showing tight correlations between sunspot activity and business cycles [3] and intriguing (but clearly misleading) studies that show tighter correlation between stork sightings and birth rates in Germany [3, 4]. Surely, that business cycles respond to solar phenomena seems as implausible as that business cycles cause sunspots, though the unwary reader of these reports could easily infer either explanation (with equal short-sightedness). Are we prepared to suspend belief in reproductive biology based on the fact that stork sightings correlated with birth rates, even with those out-of-hospital [3, 4]? Surely, the hazards of inferring causation from correlation from large data sets, which are substantial as discussed here, are exaggerated when the correlation is with observations from a single individual, as is the case in the current case report [1]. Importantly, the authors who are distinguished scholars of alpha-1 antitrypsin deficiency, acknowledge the impossibility of inferring from this observation that augmenta-

tion caused the patient's asthma to stabilize. Not stated explicitly in the paper but worthy of an important disclaimer in my view is that readers should not construe this observation as justifying use of augmentation therapy to treat asthma. Said more strongly, based on currently available information about the therapeutic effects of augmentation therapy, I believe that the critical reader will avoid any temptation based on "stork-birth rate reasoning" to prescribe augmentation therapy for asthma in PI\*MZ (or any alpha-1 antitrypsin deficient) individuals.

What then, does the current report offer? The report surely emphasizes the need for additional research regarding augmentation therapy and extends the range of issues for this research. Indeed, despite official recommendations [5], the weight of supportive observational data [5-7], and a concordant trend in the two available randomized placebo-controlled clinical trials [8, 9], the fundamental question of whether augmentation therapy slows the rate of emphysema progression in individuals with severe deficiency of AAT (i.e., PI\*ZZ) remains the subject of debate among some. Whether augmentation therapy confers benefit for fibromyalgia in AAT deficient individuals (as has been suggested by one of the authors of the current report [10]) or for panniculitis [11, 12] as has been reported in a few individuals, remains equally unclear and in need of definitive study. This report adds an intriguing question to the list of questions warranting rigorous study regarding the effects of augmentation therapy, i.e., could augmentation therapy offer benefit for refractory asthma in individuals with severe or even mild AAT deficiency (i.e., PI\*MZ individuals)?

However lofty the articulation of these questions seems, formidable challenges to conducting rigorous studies to demonstrate causality in alpha-1 antitrypsin deficiency persist. For example, though AAT deficiency is common, it is severely under-recognized [13-15] so that assembling sub-

jects in sufficient numbers to conduct adequately powered trials remains a daunting task, even in the face of huge support for research from the community of AAT deficient individuals (e.g., through the Alpha-1 Foundation [16], the Alpha-1 Association, the Alpha-1 International Registry, and other groups). In the context of the challenges of conducting clinical research regarding alpha-1 antitrypsin deficiency, provocative reports like this one remind us of the pressing need for the scientific, patient, and funding communities to unite in this effort.

Finally, why might the current intriguing case report also be troubling? As exciting and provocative as the observation that augmentation therapy was temporally associated with improvement in this single PI\*MZ patient's asthma, the report invites the risk that uncritical readers will infer causality and will be tempted to also prescribe augmentation for asthma control. Indeed, similar concern about the use of augmentation therapy for PI\*MZ individuals has recently prompted a cautionary statement by the Medical and Scientific Advisory Committee of the Alpha-1 Foundation which strongly discourages the use of augmentation therapy for PI\*MZ individuals with emphysema [17]. The proscription of augmentation therapy in this specific setting was based on the lack of available supportive evidence, the biologic implausibility of benefit for emphysema in the setting of PI\*MZ alpha-1 antitrypsin deficiency, the small (but not non-existent) risk associated with augmentation therapy, and the large current cost [18, 19], which can threaten insurance ceilings in some settings. Given this concern, the best possible effect and outcome from this report would be, on the one hand, to prompt curiosity and rigorous study of the issue and, on the other hand, to avoid the flawed temptation to similarly prescribe augmentation therapy based on the evidence offered by this single observation. After all, as every self-respecting clinician knows, however tight the correlation between stork sightings and birth rates, storks really aren't responsible for new babies.

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