It is unfortunate that pulmonary vein stenosis was only available as a diagnostic designation for a subset of the cohort in the PC4 database so that this diagnosis could not be included in the multivariate model. This disorder, although uncommon, can be extraordinarily difficult to manage, with a high risk of mortality (up to 30%) as described by the authors.

In summary, Morell and colleagues, in what is a first look at patients with PH admitted to PCICUs, bring to light the challenges and risks these patients face as a result of their PH. This work shows the formidable effect pulmonary vascular disease can have on outcomes and the role various therapeutic interventions may have on mortality risk. It's an exciting first start for providing insight into patient stratification for mortality in the PCICU and opens the door for future studies looking at patients following cardiac surgery, cardiac transplant, and other interventions. ■

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Innate Immune Training for Prevention of Recurrent Wheeze in Early Childhood

Severe lower respiratory tract infections (sLRIs) in early childhood with accompanying wheezing symptoms represent significant causes of hospital admission, particularly during infancy and the preschool years, and moreover, the repeated occurrence of these episodes in individual children is associated with markedly enhanced risk for their subsequent development of persistent asthma (1). Treatments to protect against these infections are extremely limited given the low availability of vaccines against relevant viral pathogens and the generally modest clinical benefits that appear achievable in this age group with currently available antiinflammatory drugs (2). The paucity of such treatment options has impeded the development of effective preventive strategies targeting the long-term sequelae of these infections, particularly asthma. However, recent findings, including clinical trial data published in this issue of the *Journal* by Nieto and colleagues (pp. 462–472), point toward a new therapeutic approach based on the principle of "Innate Immune Training (IIT)," which could radically impact this picture (3). This phenomenon was first recognized in infectious disease animal models as

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a prolonged state of "cell mediated acquired resistance" to multiple secondary pathogens that can develop after a primary infection or exposure to inert bacterial-derived stimuli (4). More recently, this has been demonstrated to involve a combination of epigenetic, metabolic, and functional reprogramming of innate immune cells, the end result of which is now commonly termed Trained Immunity or Innate Immune Memory (5, 6). Moreover, a number of lines of investigation suggest that the perinatal period preceding the final phase of environmental exposure–driven immune system maturation may represent the life phase during which susceptibility to these IIT effects is maximal (5, 7).

This principle has been tested by Nieto and colleagues (3) in a randomized placebo-controlled clinical trial employing 120 preschool children at high risk of infection-associated recurrent wheeze by virtue of personal history of three or more such episodes in the previous year. Children sensitized to local aeroallergens were excluded in an attempt to narrow the focus onto wheezing events associated directly with infections. The subjects were treated daily for 6 months with a polybacterial preparation (MV130) comprising a mixture of six heat-inactivated common bacterial pathogens delivered orally/sublingually, with intensive clinical monitoring over the ensuing 12 months after treatment commencement. The principal endpoint measures, notably, the number of wheezing attacks (WAs; primary outcome) and median time to first WA after treatment commencement, together with the designated secondary outcomes (total number of days with WA, mean duration of WA, symptom scores, and medication scores), were all highly significantly reduced across both the treatment and 6 month follow-up periods, consistent with successful treatment-mediated IIT.

The magnitude and consistency of these interrelated treatment effects are impressive, but a number of issues that were not addressed in detail in the study need further investigation. First, although this study focused on the <3-year-old age range, the Treatment subgroup comprised only ~3% infants (<12 mo), and it is now understood that the functionality of the innate immune system differs substantially during this very early life phase relative to later in childhood (7); the latter likely underpins the increased susceptibility of infants to sLRI, and hence the issue of whether this specific subgroup will be equivalently responsive to MV130 treatment remains unresolved. Likewise, the exclusion of allergen-sensitized subjects from the study is also problematic given that children who express the "early sensitization" phenotype appear to also manifest the highest susceptibility to the asthma-promoting effects of infant/preschool sLRI (1, 8, 9), which may be a reflection of interactions between T helper cell type 2–associated and antiviral pathways that can result in more intense airways inflammation in atopic children during respiratory infection episodes (1, 10), and it is thus important to establish whether this large subgroup of high-risk children are protected by MV130 treatment. It would also be of interest to examine the extent to which the protective effects of MV130 treatment vary across the spectrum of common early childhood respiratory viral pathogens, and likewise across the spectrum of (nasopharyngeal) bacterial pathogens, given the demonstrated importance of the latter in promoting the spread of viral infections from the upper to the lower respiratory tract (11).

Notwithstanding these limitations, the findings of Nieto and colleagues (3) are consistent with a growing body of evidence supporting IIT as a valid therapeutic approach toward reducing the pathological impact of sLRIs during the high-risk early childhood period. In this regard, it is important to note that the agent employed in their study (MV130) is not entirely unique but instead represents the latest addition to a class of microbial-derived immunomodulators in current clinical usage, particularly (but not exclusively) in pediatrics, which are based on polybacterial lysates (12). This class of therapeutics is dominated by the agent OM85, which is derived from eight major bacterial respiratory pathogens and has been in widespread clinical use for over 30 years in Europe and South America for protection of at-risk young children and adults against sLRIs and associated symptoms (reviewed in References 7 and 12). In addition to multiple investigations in older children and adults (12), recent studies employing OM85 have demonstrated a reduction in sLRI frequency and severity in preschool and early school age children (13), similar to that achieved with MV130 (3), and, importantly, have also demonstrated comparable safety/efficacy in infants preselected on the basis of high risk for atopy/asthma (14). OM85 is also in current use in a large NIH-funded multicenter trial (https://clinicaltrials.gov/ct2/show/NCT02148796) targeting similar outcomes. In addition, a number of other polybacterial lysate-based immunomodulators are available, which have been tested in a more restricted range of laboratory/clinical settings relative to OM85, and, to varying degrees, these also display innate immune stimulatory properties (12).

Current understanding of the precise mechanisms by which IIT agents mediate their effects in children is incomplete and relies principally on indirect *in vitro* observations (12). More comprehensive whole-animal data are available from experimental models, which collectively point toward myeloid precursor populations in bone marrow as the primary targets for OM85-mediated IIT effects (7, 15), likely responding to multiple TLR ligands present in this agent (9). This may account for the similarity in clinical response profiles in children evident in the recent trial results reported for OM85 (13, 14) and MV130 (3), both of which are derived from TLR ligand–rich mixed bacterial lysates.

It is tempting to speculate that these findings collectively point toward a new treatment paradigm for the protection of at-risk infants/preschoolers against the acute and long-term effects of sLRIs, particularly for the early postnatal period, which precedes functional maturation of the adaptive immune functions that underpin conventional (specific) vaccine responsiveness (5). However, ultimate achievement of that goal would require more precise characterization of the pediatric clinical settings in which IIT is maximally effective and more detailed understanding of the underlying mechanism(s) of action, both of which could underpin the development of more effective treatment regimens based on the currently available IIT agents and the future development of more readily standardized treatment agents. ■

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