

Lost in translation: Evaluating traditional Chinese medicine by western standards

In this issue of *Pediatric Investigation*, Xu et al.¹ report a study comparing two medications with immunomodulatory properties in the treatment of pediatric recurrent respiratory tract infections (RRTI). Pidotimod is a synthetic dipeptide introduced in the 1990s,² while Yupingfeng (YPF) is a traditional Chinese medicine (TCM). TCM has roots as early as the 14th century BCE. In the west, it certainly has its skeptics. A 2007 editorial in *Nature* referred to it as “largely just pseudoscience, with no rational mechanism of action for most of its therapies.”³ One issue is that TCM integrates spirituality in ways that western medicine does not and relies on a systematic approach based not on anatomy, physiology, or knowledge of cellular and molecular pathways, but on concepts such as the body’s vital energy (“qi”) circulating through channels called meridians.⁴ The various diagnostic modalities take years to learn. The radial pulse can be palpated in three locations on each arm, in both deep and superficial ways, resulting in 12 pulse points. Abnormalities of the tongue map to different internal organ abnormalities and are evaluated, for moisture, coating, and vitality. These practices are simply not components of the western physical examination. Another issue is that many of the outcomes of TCM studies rely not on symptoms with which Westerners are familiar, but on others such as improvement in “deficiencies of qi,” “exterior deficiency syndrome,” and “aversion to wind.” These outcomes can be lost in translation.

On the other hand, TCM has attracted great interest from western practitioners of medicine because of its holistic approach to the patient. While western medicine can also be holistic in the sense of treating the whole patient and not just his or her illness, in a philosophic sense, western medicine tends to be more reductionist than TCM.⁴ Whereas holism looks for “downward causation,” considering systems as more than the sum of their parts, reductionism looks for upward causation, suggesting that the whole

cannot be understood without an intricate working knowledge of individual parts. Thus, holism tends to be more mechanistically agnostic. Classical pharmacology, or forward pharmacology, has traditionally been the basis of discovery of new drugs. Compounds are screened in cellular or animal models to identify compounds that cause a desirable change in phenotype. Only after the compounds are discovered is an effort made to determine the biological targets of the compounds. The evolution of TCM holism can, in a sense, be thought of as prolonged forward pharmacology occurring over millennia, a sort of pharmacologic evolutionary “survival of the fittest.” By contrast, reverse pharmacology is more reductionist, hypothesizes that certain biological targets are disease modifying, and screens for compounds that modify these targets to see if they have a therapeutic effect. This is the basis of high-throughput screening, which can result in the screening greater than 100 000 compounds per day.

The study by Xu et al.¹ is a large multicenter, randomized, double-blind, noninferiority clinical trial. This study had 3 arms: YPF granules (experimental drug), pidotimod oral solution (positive control), and placebo. The children were treated for 8 weeks and followed-up for 52 weeks. The primary outcome was RRTI control rate. Secondary outcomes included effect on clinical symptoms according to TCM, safety and cost. Noninferiority evaluation was performed to compare YPF to pidotimod. They report a significant treatment effect of both YPF and pidotimod compared to the placebo group. There were no significant differences in TCM outcomes between the YPF and pidotimod treated groups. There were no major side effects. In addition, YPF granules were more cost-effective than pidotimod.

This study is valuable, as TCMs are not often as fully documented for efficacy and safety as more conventional therapies. The study included 351 children enrolled in

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13 different Chinese hospitals and supports evidence from previous smaller and single-centered studies. The authors designed a rigorous study, which is strengthened by its methodology: by being a randomized, controlled, and double-blinded trial, it ensures a fair comparison and helps reduce bias. Double simulation technology allowed the placebo arm to use simulants that mimicked the active drugs in appearance and odor, improving the double-blind. Having a large sample size helps achieve higher power and reduces type-2 error.⁵ This study is also reinforced by its intention-to-treat (ITT) analysis. Randomization studies have the risk of loss to follow-up or noncompliance and if these participants are excluded in the data analysis it may affect statistical results leading to erroneous conclusions. ITT analysis is a strategy that includes all participants that were initially assigned in each treatment group regardless of adherence, treatment received, or withdrawal from the study. This has several advantages: it helps maintain the benefit of randomization and prevents allocation bias. Having a large enough sample helps maintain an equal distribution of characteristics between the different treatment groups and minimizes confounding between them. In addition, ITT mitigates bias due to unequal drop-out rates between groups. If more subjects drop out of the treatment arm because of side effects or lack of efficacy, for example, the treatment can seem more effective than it actually is, because the subjects in whom it is not effective are under-represented.

What are the possible biologic mechanisms underlying the therapeutic benefits of YPF and pidotimod? Both drugs are considered immunomodulatory. Immunostimulants are biologically active substances of natural and synthetic origin that have been found to boost the immune system through different mechanisms of action.⁶ In a Cochrane review involving 35 studies and 4060 participants, immunostimulants reduced the number of acute respiratory tract infections compared to a placebo.⁷ Pidotimod is a synthetic peptide molecule (3-L-pyroglutamyl-L-thiazolidine-4-carboxylic acid) that has been used to help prevent recurrent respiratory infections.^{6–8} Studies in mice and humans have shown that pidotimod stimulates both innate and adaptive immunity by increasing dendritic cell maturation, releasing proinflammatory cytokines leading to differentiation of T helper (Th) cells to Th1 cells and increasing natural killer cells, macrophages, and salivary IgA. YPF includes a mixture of 3 medicinal herbs, Astragali Radix (Huangqi), Atractylodis Macrocephalae Rhizoma (Baizhu), and Saposhnikoviae Radix (Fangfeng). It has been used for centuries in TCM and is currently used for treatment of asthma, bronchitis, allergic dermatitis and urticaria. Animal and *in vitro* studies have reported immunomodulatory properties including reduction in tumor necrosis factor alpha, interleukin-6, mucus secretion and modification


of factors such as MUC5A which are involved in producing inflammatory cells and cytokines, T-cell differentiation, and serum levels of IgA, IgG, IgM, and CD3⁺ T cells.⁹

One of the possible limitations in any study evaluating treatment for RRTI in children is whether we are actually treating infection. There is a broad overlap in symptoms between respiratory infections and pediatric asthma, especially in preschool children, with wheezing as a prominent component. One can wonder whether the TCM symptom of “aversion to wind” is in fact a reflection of cold air induced wheeze, a well-described asthma symptom. Immunomodulatory medications could possibly affect outcomes in both asthma and RRTIs, so the definition of RRTIs is of paramount importance. The diagnostic criteria used for RRTIs in this study are described in a Table in the Xu article, taken from a publication in the *Chinese Journal of Pediatrics* by the Subspecialty Group of Respiratory Diseases, The Society of Pediatrics, Chinese Medical Association.¹⁰ However, a Medline search for this important position paper found no version translated to English. This is another example of how the understanding of TCM in the west can be not lost in translation but literally lost due to no translation.

While therapeutic mechanisms are of relevance, treatments may still be effective even if a biological basis is unknown. For example, hypertonic saline nebulization and medications that modify salt and water transport through chloride and sodium channels in respiratory epithelial cells are well-established treatments for cystic fibrosis based on a detailed understanding of the molecular structural and functional activities of these channels. However, environments with high atmospheric salt concentrations, from the coastal surf of Australia to the salt caves of Salzburg, Austria (“speleotherapy”), were recognized to be beneficial well before these therapies were introduced or mechanistically understood. Just because we don’t understand how a drug works, it doesn’t mean that it doesn’t work; it just means we don’t understand how...yet.

Forward and reverse pharmacology are not mutually exclusive, but rather iterative. Only by identifying compounds and subsequently their biological targets can further compounds be subject to high throughput screening to see if those targets can be modified. In much the same way, TCM and western medicine are not mutually exclusive. While TCM may value empiric results over mechanisms, the results of studies such as that of Xu et al. may lead to further understanding of mechanisms encouraging the discovery of new therapies. Although the pathophysiologic concepts of TCM and western medicine may well be mechanistically irreconcilable, empiric findings of beneficial effects of therapeutics can still be rigorously tested. The trickiest part may not be reconciling the presumed mechanisms, but defining

outcomes that both disciplines can agree upon. Still, studies like that of Xu et al. are an excellent step toward addressing western skepticism.

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CONFLICT OF INTEREST

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