

The spectrum of chronic rhinosinusitis therapy: from irrigation to the off-target effects of biologics

The collection of articles in this issue of the *International Forum of Allergy and Rhinology (IFAR)* truly reflects the broad translational state of rhinology, covering computational fluid dynamics (CFD) modeling, inflammatory cytokine profiling, and novel drug eluting stents, all in the efforts to improve outcomes for our patients. Additionally, a new subtype of chronic rhinosinusitis (CRS) resulting from anti-tumor necrosis factor α (anti-TNF α) biologic therapy is characterized, stressing the importance of vigilant surveillance of patients receiving “biologics” for off-target sequelae.

Topical pharmacotherapy has been a game changer in the management of CRS and has become the pillar of therapeutic intervention; several studies in this issue focus on varied aspects of optimizing this treatment modality. Husain et al.¹ compared several bottle-cleansing techniques and solution disinfection protocols to maintain hygienic irrigations. They compared treating contaminated bottles with detergent or microwaves as well as several different treatments of the water against several bacterial species. With the exception of reverse osmosis treatment of water, all the modalities and combinations tested were effective, with robust bacterial disinfection. However, the issue of disinfecting the irrigation solution has attracted attention recently because of rare instances of amoebic contamination with resulting amoebic encephalitis,^{2,3} and this article does not address amoebic disinfection. Jiao et al.⁴ evaluated the effects of hypertonic solution (3%) on human sinonasal epithelial cells and confirmed prior findings of significant epithelial toxicity. Although this modality is used in cystic fibrosis (CF) patients with the rationale of increasing mucus hydration through osmotic forces, the evidence supporting this practice is of low quality,⁵ and in the non-CF individual is most likely not warranted. de Gabory et al.⁶ used CFD simulation to compare large-volume irrigation to continuous spraying and, as expected, found that large volume with both gravity and positive pressure delivers more solution in a faster manner



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than continuous spray. Barham⁷ evaluated different frontal sinus surgical techniques in cadavers for improving topical irrigation delivery to the frontal sinus, confirming prior studies^{8,9} of superior irrigation of the frontal sinus with the Draf III procedure. Finally, Lim et al.¹⁰ evaluated a biodegradable stent coated with ciprofloxacin and azithromycin as a putative treatment for *Pseudomonas* sinusitis. They achieved very favorable in vitro diffusion kinetics as well as impressive in vitro antibiofilm activity; such a stent will be needed as multidrug-resistant *Pseudomonas* is encountered more often in CRS patients.

Olfactory dysfunction is a common complaint for CRS patients. In efforts to determine non-CRS contributors to olfactory dysfunction, Schlosser et al.¹¹ incorporated a control (non-CRS) population in a large (nearly 400 subjects), multicentered, prospective study. As expected, in patients with CRS with nasal polyposis (CRSwNP) the main driver of olfactory dysfunction was the polyps, but interestingly, they found that olfactory dysfunction in CRS without nasal polyposis (CRSSNP) has major contributors, such as diabetes, asthma, and age, which are more systemic than the sinonasal inflammatory processes. This finding is somewhat surprising and counterintuitive and should be incorporated into discussions of expectations for restoration of olfactory function in CRSSNP patients.

In the last 5 years, tremendous efforts by multiple groups have attempted to better define CRS subtypes through tissue/mucus/blood endotyping for guiding “individualized” therapeutic intervention as well as prognosticating outcomes. Along this approach, Chowdhury et al.¹² undertook a large prospective endotyping analysis of nasal mucus collected at the time of sinus surgery; they included 17 cytokines and followed patients for an average of 10 months postoperatively. Their results suggest that operative mucus levels of TNF α , interleukin 2 (IL-2), IL-5, and IL-13 are predictive of postoperative improvement in 22-item Sino-Nasal Outcome Test (SNOT-22) scores.

Biologic therapy encompasses utilizing designer fusion antibodies to “remove” offending biologic inflammatory signaling molecules such as cytokines. Dupilumab (anti IL-4/13 receptor antibody) was recently approved by the U.S. Food and Drug Administration (FDA) for treatment of CRSwNP.¹³ Although biologics have a relatively safe

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profile, long-term sequelae of “removing” an endogenous inflammatory signaling molecule are still being appreciated. Papagiannopoulos et al.¹⁴ describe a subtype of CRS found in patients who had received biologic therapies targeting TNF α —therapies that have been on the market for approximately 20 years. They term this subtype CRS α i, which is histopathologically characterized by mucosal ulceration

and fibrosis, as well as the paradoxical presence of Charcot-Leiden crystals, but decreased eosinophils. This last study emphasizes that as more patients are treated with biologic therapies, clinicians must be diligent, with careful follow-up for “off-target” sequelae.

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