asthma had a less robust response to the pneumococcal vaccine compared to CRSsNP patients without asthma, suggesting that CRSsNP asthmatics may have an impaired mucosal response to *S. pneumoniae* exposure as well as an impaired systemic polysaccharide antibody response. In contrast, within the CRSwNP group, there was no significant difference in the number of protective post-immunization titers based on the presence of asthma, suggesting no difference in humoral response.[946] Finally, in their systematic review, Mazza et al. appreciated no association between immunodeficiency and the presence of polyps.[1284] They report, however, that the presence of polyps may predict recalcitrant disease in patients with primary immunodeficiency.[1284]

The evidence linking immunodeficiency to CRSwNP is contradictory. In an effort to uncover all possible etiologies, some experts have recommended testing for immunodeficiency in refractory CRSwNP patients. The main reason for this recommendation is that immunodeficiency may alter treatment considerations. In addition, this knowledge of an immune explanation alone may be a relief to the patient with recurrent sinus problems. Further well-designed studies to evaluate the pathophysiology of immunodeficiency and CRSwNP are needed.

Immunodeficiency as a Contributing Factor for CRSwNP

Aggregate Grade of Evidence: C (Level 3: 2 studies; level 4 studies: 7; Table X-15).
Benefit: Identifying patients with PID allows for the opportunity to treat a subset of patients who will respond to Ig replacement therapy.
Harm: Procedural discomfort; Identifying and treating incidental findings or subclinical conditions that might not require independent therapy.
Cost: Procedural and laboratory cost.
Benefits-Harm Assessment: Balance of benefit over harm.
Value Judgments: Evidence for immunodeficiencies in CRSwNP patients is contradictory and low-level.
Policy Level: Option.
Intervention: Patients with CRSwNP may be evaluated for the presence of an underlying PID.

X.C.16 | Contributing Factors for CRSwNP: Genetics and Epigenetics

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.C.15.

X.C.17 | Contributing Factors for CRSwNP: Aspirin (Aspirin Exacerbated Respiratory Disease)

Aspirin-exacerbated respiratory disease (AERD), commonly referred to as Samter's triad, and increasingly recognized as nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (NSAID-ERD) in Europe, is characterized by recurrent CRSwNP, asthma, and distinctive respiratory reactions to aspirin and other non-specific NSAIDs.[1516–1519] Prevalence rates of AERD among the general population have been estimated at 0.6% to 2.5%, while rates among patients with CRSwNP approach 10%, and are higher in tertiary care populations.[198,1520,1521] The components of AERD do not typically present at once, and the initial presenting condition may vary. Roland et al. found the most common sequence of presentation, found in 36% of AERD patients, is asthma, followed by nasal polyps, followed by NSAID hypersensitivity.[1522]

Though the clinical presentation of AERD is well-described, the exact pathophysiologic mechanism of AERD is less clear. Nonetheless, it has long been recognized that dysfunction in the arachidonic acid metabolism pathway is fundamental to disease development. NSAIDs affect the arachidonic acid pathway and cause inhibition of the cyclooxygenases (COX), which are necessary for metabolizing arachidonic acid into prostaglandins.[1523] Due to this inhibition, the lipoxygenase pathway is further activated during NSAID-induced reactions, which leads to an imbalance of anti-inflammatory prostaglandins (PG) and proinflammatory LTs. On top of this physiological inhibitory effect, individuals with AERD are thought to have reduced activity of the constitutively expressed COX 1 isoenzyme, as well as increased LT receptor expression. Due to dysregulation in arachidonic acid metabolism, the PG/LT imbalance in these patients is altered to favor a proinflammatory state that fuels the inflammatory cascade characteristically seen in patients with AERD. The activation of eosinophils, mast cells, and basophils likely leads to the release of cysteinyl leukotrienes (cysLTs), prostaglandin D_2, histamine, tryptase, and the stimulation of innate type 2 immune responses.[1518,1519,1524] Pathological evaluation of nasal polyps in patients with AERD demonstrates intense eosinophilic infiltration and activation.[1525] Histopathological analysis reveals that the NP in patients