



Special Series

Drug Allergy

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A new *Annals* feature in 2018, “From the Pages of Allergy-Watch” is devoted to publishing synopses of Allergy and Asthma literature relevant to a topic of emphasis. These unbiased synopses and comments by our Editors have been

previously printed in the AllergyWatch bimonthly newsletter, and it is our hope that presenting carefully selected article summaries and comments in the *Annals* will serve as a valuable educational resource for practicing allergists.

For this edition of Annals, focusing on Drug Allergy, From Pages of Allergy Watch highlights reviews of articles that concentrate on reactions to medications. The initial report investigates the impact of PPI and antibiotics that can impact the microbiome on the development of allergy in children. The next review raises the

concern about risk for dementia with H1 antihistamines. The potential risk for complications of infections in patients with penicillin allergy is reviewed in the next article. And lastly, a new strategy for management of patients with radio-contrast reaction is reported.

Think Twice before Prescribing Acid Suppressive Medications or Antibiotics to Infants

Early-life exposure to medications, including acid-suppressors and antibiotics, may affect childhood allergy risk by altering the microbiome. This study evaluated the use of acid-suppressive and antibiotic drugs during infancy for association with the risk of allergic diseases in early childhood. The study included 792,130 children from the US Department of Defense's TRICARE Management Activity Military Health System database. All were born between 2001 and 2013, with continued enrollment from within 35 days of birth to at least age 1 year. Infants with an initial hospital stay of more than 7 days or with allergic conditions diagnosed before 6 months of age were excluded from the study. During the first 6 months of life, a histamine-2 receptor antagonist (H2RA) was prescribed for 7.6% of infants, a proton pump inhibitor (PPI) for 1.7%, and an antibiotic for 16.6%. These exposures were analyzed for association with diagnosis of allergic diseases at a median follow-up of 4.6 years. Other than seafood allergy, risks of all allergic conditions evaluated were increased for children with exposure to H2RAs or PPIs. For food allergy, adjusted hazard ratios (HRs) were 2.18 for H2RA and 2.59 for PPI exposure. The increase in food allergy

risk with acid-suppressive medications was dose dependent. Both classes of acid-suppressing drugs were also associated with increased risks of medication allergy, anaphylaxis, allergic rhinitis, and asthma. Exposure to antibiotics during infancy was associated with increased risks of asthma, HR 2.09; allergic rhinitis, HR 1.75; anaphylaxis, HR 1.51; and allergic conjunctivitis, HR 1.42. Antibiotic prescription was associated with increased risks of cow's milk and egg allergy, but not peanut or seafood allergy. Infants prescribed acid-suppressive or antibiotic medications in the first 6 months of life are more likely to develop childhood allergic diseases. The strongest associations are noted for acid-suppressing drugs and the risk of food allergies. Further studies will be needed to confirm the causal nature and determine the mechanism of these associations.

Comments from Chitra Dinakar, MD: The question of whether using microbiome-perturbing medications in infancy alters the subsequent risk of allergic diseases bothers all of us. In the largest retrospective cohort childhood study to date, the hazard of developing an allergic disease was significantly increased in those receiving acid-suppressive medications or antibiotics during the

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first 6 months of life. Adjusted HRs in infants prescribed H2RAs/PPIs and antibiotics were highest for food allergy and asthma, respectively. The take-home message is that acid-suppressive medications and antibiotics for infants should only be prescribed in situations of unequivocal clinical benefit.

Anticholinergic Agents and Dementia Risk

Anticholinergic drugs, which block the neurotransmitter acetylcholine, are used for a wide range of indications, including allergic diseases. Previous studies have suggested that prolonged exposure to anticholinergic drugs might be associated with cognitive decline or dementia. The association between anticholinergic medications and dementia risk was assessed using a large primary care database. The case-control study included 40,770 older adults with dementia, identified from the UK Clinical Practice Research Datalink. Cases were matched to 283,933 controls without dementia. Exposure was assessed using the Anticholinergic Cognitive Burden (ACB) scale, considering exposure to different categories of anticholinergic drugs over 4 to 20 years before dementia diagnosis. Associations with incident dementia were assessed, with adjustment for potential confounders. At least 1 drug with an ACB score of 3—indicating “definite anticholinergic activity”—was prescribed to 35% of dementia cases and 30% of controls. Any anticholinergic drug in this category was associated with an increased risk of dementia: adjusted odds ratio 1.11. Dementia risk also increased with higher average ACB score. By indication, dementia risk increased with greater exposure to antidepressant, urologic, and antiparkinsonian drugs with an ACB score of 3, although not with exposure to gastrointestinal drugs. The associations remained significant for exposure 15 to 20 years before

Mitre E, Susi A, Kropp LE, et al. Association between use of acid-suppressive medications and antibiotics during infancy and allergic diseases in early childhood. *JAMA Pediatr.* 2018; 172:31803-31815.

dementia diagnosis. Analysis restricted to new users showed little change in the strength of the associations, particularly for antidepressant and urologic drugs, with an ACB of 3. Exposure to some classes of anticholinergic medications is strongly associated with future risk of developing dementia. Other anticholinergics do not appear to be related to dementia risk, whereas the association remains unknown for some of these drugs. The authors suggest that clinicians should consider the long-term cognitive effects of anticholinergic drugs when performing risk-benefit analysis.

Comments from David Michael Lang, MD: This case-control study extends previous findings associating exposure to agents we prescribe—particularly for refractory chronic urticaria—with an increased risk of developing dementia. The study associates this risk with antidepressant medications and reports a “trend” for risk with antihistamines that penetrate the blood-brain barrier and can cause acute delirium. These findings are clearly relevant for interpretation of recommendations for management of chronic urticaria (*J Allergy Clin Immunol.* 6 September-October 2018). Advancing patients with a refractory course to a trial of doxepin will need to be considered more carefully from the standpoint of balancing potential for benefit with potential for harm.

Richardson K, Fox C, Maidment I, et al. Anticholinergic drugs and risk of dementia: case-control study. *BMJ.* 2018; 360:k1315.

Morbidity of Penicillin Allergy

Self-reported penicillin allergy leads to patients being prescribed more broad-spectrum antibiotics, potentially leading to infection with drug-resistant bacteria. This population-based study examined the association between penicillin allergy and risk of infection with methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile*. Using the UK Health Improvement Network database, the researchers identified 64,141 adults with penicillin allergy and 237,258 matched controls. Both groups were free of previous MRSA or *C difficile* infection. The association between newly documented penicillin allergy and the incidence of these drug-resistant infections was evaluated. Use of beta-lactam and alternative antibiotics was evaluated as well. Over a mean 6 years of follow-up, MRSA was diagnosed in 1365 patients and *C difficile* in 1688. The incidence of both drug-resistant infections was increased among patients with penicillin allergy: adjusted hazard ratio 1.69 for MRSA and 1.26 for *C difficile*. Patients with penicillin allergy had increased use of macrolides, clindamycin, and fluoroquinolones: incidence rate ratio 4.15, 3.89, and 2.10, respectively. These alternative antibiotics were associated with increased risks of MRSA or *C difficile*. Use of beta-lactam alternatives mediated 55% of the effect of penicillin allergy on MRSA risk and 35% of the effect

on *C difficile* risk. Patients with recorded penicillin allergy are at higher risk of incident MRSA and *C difficile*, and these risks are largely related to the increased use of alternative antibiotics. The researchers conclude, “Systematic efforts to confirm or rule out the presence of true penicillin allergy may be an important public health strategy to reduce the incidence of MRSA and *C. difficile*.”

Comments from David Michael Lang, MD: When patients who furnish a history of allergy to penicillin or a penicillin-like drug require antibiotic administration, an alternative antibiotic (eg, quinolone, macrolide, or vancomycin) is commonly prescribed. This important study provides additional evidence that these alternative agents are associated with heightened risk for untoward effects: increased rates of MRSA and *C difficile*. More frequent allergy/immunology evaluation, including immediate hypersensitivity skin testing to penicillin reagents, can lead to improved outcomes. This is an important opportunity for our specialty to address an imminent public health challenge.

Blumenthal KG, Zhang Y, Walensky RP, Choi HK. Risk of methicillin resistant *Staphylococcus aureus* and *Clostridium difficile* in patients with a documented penicillin allergy: population based matched cohort study. *BMJ.* 2018; 361:k2400.

Pretreatment for Contrast Procedures: 5-hour vs 13-hour Regimen

Patients at risk of allergic-like reactions to contrast media may receive oral corticosteroid pretreatment, most commonly in a

13-hour regimen. Accelerated intravenous corticosteroid regimens may be used in urgent or other situations, despite a lack of

supporting evidence. This study compared the rate of allergic-like breakthrough reactions to contrast media in patients receiving a 5-hour intravenous corticosteroid regimen vs the standard 13-hour oral regimen. The retrospective analysis included 202 patients who received an accelerated 5-hour intravenous corticosteroid regimen before receiving low-osmolality, iodine-based contrast media for computed tomography examination. A comparison group included 626 patients receiving the 13-hour oral regimen; all patients had a previous allergic-like or unknown reaction to contrast media. The breakthrough reaction rate was compared between groups. Breakthrough reactions occurred in 2.5% of patients receiving the 5-hour intravenous regimen compared with 2.1% with the 13-hour oral regimen. The upper limit of the confidence interval for the difference between groups was 3.7%, which was under the specified noninferiority margin of 4.0%. Of the total of 4 breakthrough reactions, all were of equal or lesser severity than the initial reaction. A 5-hour intravenous corticosteroid premedication regimen is “at least not substantially less effective” than the standard 13-hour oral regimen in patients with prior contrast reactions. The authors

suggest that the accelerated IV regimen can be considered for patients with competing medical priorities, including emergency or inpatient examinations.

Comments from David Michael Lang, MD: Allergy/immunology physicians routinely recommend pretreatment with a 13-hour diphenhydramine and prednisone regimen for patients with prior reactions. However, this may be associated with harmful consequences for inpatients—including higher rates of infection and prolonged length of stay (*Radiology*. 2016;279:492-501)—that may exceed benefit. This study offers evidence that an accelerated 5-hour regimen is noninferior to the standard 13-hour regimen for risk of breakthrough reactions. However, the study was underpowered for moderate and severe reactions. Additional studies with more clearly defined patient selection will be required before we alter our recommendations for a 13-hour pretreatment regimen for patients with prior anaphylactoid reactions.

Mervak BM, Cohan RH, Ellis JH, et al. Intravenous corticosteroid premedication administered 5 hours before CT compared with a traditional 13-hour oral regimen. *Radiology*. 2017; 285:425-433.