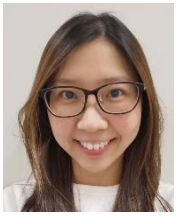
JSA/WAO Joint Congress 2020 – Conference Highlights



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The Japanese Society of Allergology (JSA) co-organized the XXVII World Allergy Congress (WAC2020) with the World Allergy Organization (WAO) last September of 2020 in their first virtual platform due the ongoing COVID-19 pandemic. As an immunology and allergy trainee, the experiences, knowledge, and appreciation for the field I have gained, albeit not meeting these academic giants in person, were invaluable. I would like to thank the Hong Kong Institute of Allergy again for the generous nomination for attending this conference.

A particularly memorable keynote speech was delivered by the distinguished Professor Sakaguchi on the importance of regulatory T cells (Tregs) in unlocking the pathogenesis behind autoimmune diseases and cancer immunology.[1] Immunological tolerance is understood to be achieved by several mechanisms: apoptosis, inactivation and suppression of cells that recognize self-antigens, such as through Tregs. Many Treg signature genes such as *Foxp3, IL2ra (CD25), Ctla4, Ikzf2 (Helios), and Ifzf4 (Eos)* have been identified in the development of Tregs. In the classical IPEX syndrome, mutations in the FOXP3 gene have results in a plethora of autoimmune manifestations such as type 1 diabetes mellitus, enteropathy and eczema. FOXP3 is a transcription factor present in naturally occurring CD4+ Tregs responsible for activation and suppression of various downstream genes. In particular, FOXP3 suppresses IL-2 production and upregulates IL-2R. Studies showed inoculation of knockout mice with neutralization of IL-2 with anti-IL-2 antibody caused autoimmune diseases such as pancreatitis and thyroiditis.[2] IL-2 is important for Treg survival, expansion and suppress effector T cells. CTLA4, a homologue of CD28 expressed on T cells interacts with the CD80/86 on antigen presenting cells. FOXP3 upregulates CTLA-4 thereby, downregulating CD80/86 and its interaction with CD28 on effector cells required in the co-stimulation of T cell receptor. Epigenetics also play a key role in the maintenance and stability of natural Tregs that are not seen in induced Tregs despite the expression of FOXP3 protein. There were around 300 Treg specific demethylated regions in the FOXP3 gene compared with around 156,000 total methylated regions. Natural Tregs possess specific epigenetic patterns. Hence, a functional Treg needs both the FOXP3 expression and Treg type DNA hypomethylation. Strategies in upregulating Tregs to induce a dominant tolerance state have been the subject of interest in treatment of various autoimmune diseases. In-vivo expansion of natural Tregs by inhibiting the effector T cells include low dose IL-2 and rapamycin. Allergen-specific immunotherapy, such as house dust mite SLIT and SCIT, is also an example of enhancing Tregs at the mucosal level. Chimeric antigen receptor Tregs has also been used to bypass the slow process of purifying and expanding naturally occurring Tregs. Methods to convert conventional T cells into Tregs have also been studied. Both FOXP3 expression and Treg specific demethylating regions were important in maintaining functional Tregs. Akamatsu et al. found a compound that converted conventional T cells into in-vitro induced Tregs by inhibiting CDK8/9 which in turn removed the inhibition of STAT5 transcription and FOXP3 expression. Mikami et al. also found that Treg-specific demethylation could be induced by depriving CD28 signalling.[3] Abatacept, of course binds to CD80/86 on antigen presenting cells thereby reducing the CD28 signalling. This "super" induced Tregs was able to maintain Treg function even after *in vivo* transfer. On the contrary, Treg downregulation strategies can enhance immune response and promote antitumor immunity and treatment of chronic infections. Use of target immunotherapy such as monoclonal antibodies (e.g. anti-CTLA4 monoclonal antibody) strive to specifically target signals that are predominantly expressed on tumours, thereby balancing the antitumor effect and the development of autoimmune diseases.

I was also given the opportunity to share our research on piperacillin-tazobactam (PT) allergy.[4] At the time of writing, few case reports and series have been reported in the literature on PT allergies with reporting bias for more severe reactions including anaphylaxis and drug rash with eosinophilia and systemic symptoms. With the increasing and liberal use of broad-spectrum antibiotics, PT allergies have proportionately also increased. PT has broad coverage against both gram-positive and gram-negative bacteria, especially *Pseudomonas aeruginosa*, and is particularly useful in patients prone to *Pseudomonas* infections and colonization. Results from the Global Point Prevalence Survey of Antimicrobial Consumption and Resistance showed that the most prescribed antibiotic were penicillins with a beta-lactamase inhibitor, including PT.[5] Between 2015 to 2019, the use of PT prescribed in Hong Kong increased by 150%, which were consistent throughout all 7 clusters. A previous pilot study on penicillin allergy labels among hospitalized patients in Hong Kong found a surprisingly high rate of confirmed PT allergies.[6] Skin tests for PT allergies (0/3 for immediate type reactions and 0/6 for delayed type reactions) were all negative and all required drug provocation tests for confirmation. In contrast, the negative predictive value for penicillin skin tests is well quoted to be greater than 90%.[6-8] We conducted a retrospective study on reported PT allergies referred to Queen Mary Hospital between 2015 to 2020. Of 34 patients who

eventually completed full workup for suspected PT allergy, 32.4% were confirmed to be genuine allergy to PT. Only 2 patients were diagnosed by a positive skin test: one delayed-type reaction with skin test showing selective reactor to PT alone. The other patient confirmed with immediate type reaction to PT had sensitization to minor determinant, benzypenicillin and PT. We also found that confirmed PT-allergic patients were more likely to present with delayed-type reactions. Confirmed PT-allergics were less likely to have an unknown index reaction, which we know is a low risk allergy history in other penicillins.[9] Most patients referred with PT allergy labels had concomitant medical co-morbidities, with bronchiectasis and concurrent use of immunosuppressants being the most common. This is not surprising given that the use of PT in Hong Kong is mainly prescribed in a hospital setting, with patients in this high-risk cohort requiring broad spectrum antibiotics. In view of the low NPV of PT skin tests, we recommend that skin test alone cannot rule out a genuine allergy. Drug provocation test is still the gold standard for confirmation and should be done cautiously if required and referred to an allergist in non-low risk patients. Adjuvant tests such as serum for selective IgE to various penicillin groups in immediate-type reactions, lymphocyte transformation tests and patch tests for delayed-type reactions need to be further studied. In patients with immediate type hypersensitivity reactions to PT, Gallardo et al. was able to differentiate the skin test phenotypes into 3 groups: sensitization to the β-lactam ring (group 1), the lateral chain of aminopenicillins (group 2) and selective to PT alone (group 3).[10] This allows physicians to differentiate those who are likely allergic to PT alone (group 3) or proceed with further tests to look for alternative antibiotics such as workup for the carbapenem groups (group 1) and which may cross-react with cephalosporins (group 2).

PT allergies are an exception to usual penicillins (Table 1). There are several reasons attributable to the discrepancies. The proportion of PT allergies confirmed positive could be a reporting bias. PT allergies reported in our study were reported by the patients' attending physician. In contrast, previous studies on penicillin allergy labels have included patient reported labels and could reduce the accuracy of genuine reported allergies. Second, the validation and non-irritating and test concentrations for β-lactams skin tests is well established for amoxicillin, ampicillins, and cephalosporins.[11] Validation for PT skin tests were sparse in the literature at time of writing. We used the skin prick concentration of 4.5g/mL (i.e. NEAT) based on the study by Rank et al.[12] In a case series of piperacillin-induced DRESS by Cabanas et al, 8 of 8 patients had a positive lymphocyte proliferation test (as defined by a stimulation index of >3).[13] Four of 8 patients underwent IDT with readings taken immediately, 6 hours and 24 hours later. Three of 4 patients used a concentration of 2.25mg/mL, and all showed positive readings. One of 4 patients used a concentration of 0.225mg/mL but had a negative reading. We used the same intradermal concentration for both immediate and non-immediate type reactions (2.25g/mL) referenced from that study. One limitation of our study is that we did not have a reference for this concentration for intradermal test in immediate-type reactions and did not test this concentration in non-allergic controls. In retrospect, only 1 of 5 patients with confirmed immediate type HSR to PT showed a positive ST. Investigating the different IDT concentrations compared with a controlled healthy cohort to increase the concentration in hopes of increasing sensitivity of IDT whilst still being a non-irritant concentration in a comparable controlled cohort of healthy volunteers with previous tolerance to PT could be the direction for future studies. Meanwhile, physicians should beware of PT allergies, even for those with negative skin test results. Drug provocation test is still the gold standard for workup of PT allergies.

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Table 1: Comparisons between PT allergies and other penicillin allergies

	Piperacillin-Tazobactam	Penicillin
Genuine allergies after confirmation with drug provocation test	32.4%	10-20%(6, 8)
Negative predictive value of intradermal skin test	71.9%	90-98%(7, 8)
Percentage change of antimicrobial dispensed in Hong Kong overall (2018 over 2016)	17.85%[14]	Amoxicillin-clavulanate: 6.8% Amoxicillin: -3.08% Cloxacillin: -27.84% Ampicillin -30.36%