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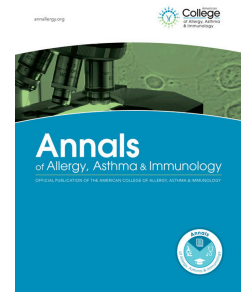
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"Drug Allergy in children and adults: is it the double X chromosome?"

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Abbreviations:

Adverse drug reactions (ADRs)

Aspirin exacerbated respiratory disease (AERD)

Bronchoalveolar Lavage (BAL), T-regulatory Cells (Tregs)

Dendritic cells (DC)

Drug Induced Anaphylaxis(DIA)

Endothelial nitric oxide synthase (eNOS)

Estrogen receptors (ERs)

Estrogen response elements (EREs)

Heat shock protein (HSP)90

Innate Lymphoid Cells (ILC)

NSAID-exacerbated cutaneous disease (NECD),

NSAID exacerbated respiratory disease (NERD) T-regulatory Cells (Tregs)

X chromosome inactivation (XCI)

X inactivation specific transcript (XIST)

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"Drug Allergy in children and adults: is it the double X chromosome?"

It is well established that autoimmune diseases, atopic conditions and asthma affect adult females more frequently than adult males. This discrepancy typically develops after childhood and affects females differently depending on their life cycle. As children, males have higher total and allergen specific IgE levels than females and are more likely to suffer from atopic disease and asthma than girls. However, as adults, this prevalence reverses and females are more likely to develop atopic conditions such as food allergies, atopic dermatitis, urticaria, angioedema and asthma.^{1,2}

Certain adverse drug reactions (ADRs) have been reported to occur more frequently in adult females or to affect them more severely.^{3,4} ADRs include all types of reactions related to drugs, including side effects, with only the minority being immunologically-mediated drug allergy, driven by adaptive and/or innate mechanisms. Most self-reported drug allergies are not true allergy and when investigated are rarely determined to be immunologically-mediated.⁵

Interestingly, both self-reported and immunologically-mediated drug allergy are more frequently observed in adult females compared to males.^{6,7}

Despite adult female predilection for drug allergy, there are few laboratory studies exploring gender specific mechanisms in atopic/allergic diseases, and most are focused on autoimmunity and asthma. Possible explanations for gender disparities in disease are multi-factorial and include disproportionate utilization of healthcare with more exposure to antibiotics/medications, genetic factors related to the X chromosome, epigenetic changes, and discrepant hormonal interactions with immune cells. This article will review the latest science and epidemiologic studies related to drug allergy in children and adults to explore possible mechanisms related to

female propensity for drug allergy. In this review, the term female focuses exclusively on the known biological differences between females and males. This focus comes with the recognition that gender is complex with a multitude of social, physical, and environmental influences.

Adverse Drug Reactions and Gender

Although over 15% of individuals self-report a drug allergy, almost 90-95% will tolerate the drug with subsequent drug challenge, meaning that the majority of self-reported drug reactions are unlikely to be immunologically-mediated drug allergy.⁵ The incidence of self-reported drug allergy is higher in females than males. First time consults for drug allergy are sought more frequently in females, with one study reporting a female to male ratio of approximately 2:1.^{3,8} This may be explained in part by adult females being more proactive than males in healthcare utilization, though gaps in healthcare for females in particular diseases do exist.⁹ Female patients also use more antibiotics, which may increase their risk of developing allergy to these medications.¹⁰ In one study by Macy and Poon, 92% of patients reporting 10 or more drug “allergies” were female with a mean age of 67 years. In fact, in this study 20% of females over the age of 80 reported an “allergy” to penicillin compared to 14.9% of males. Increasing age contributes to more antibiotic “allergy” not only because of frequent antibiotic and health care use among females but also because of very low rates of drug allergy de-labeling.¹⁰ One study by Macy et al reviewed medical records of 2,375,424 individuals who had at least 11 months of healthcare coverage during 2009, and at least 1 medical visit during 2009. 1,296,803(54%) of these participants were female and 1,078,621(45%) were male. In this sample, there were 478,330 (20.1%) members with any “allergy” reports of whom 325,381(68%) were females and 152,902 (32%) were male. This large group represents approximately 1% of the United States population who use healthcare and is therefore a good proxy for gender distribution in self-

reported drug allergy.⁷ In one registry of hospitalized patients with drug allergy, females were statistically more likely to develop adverse drug reactions than males, although there were no significant differences in the clinical manifestations and drug allergy mortality between both genders, which has been supported by further studies.^{3,11}

In contrast to drug allergy studies focusing on adult populations, when studies assess drug allergies in children, a gender difference is often not detected. The exception may be related to adverse drug reactions. One large systematic review by Smyth et al suggested that the incidence of ADRs is higher in girls with an odds ratio of 1.13.¹² However, in general when children are assessed using parental questionnaires alone and/or further evaluated with skin testing and drug provocation testing, there is no consistent female predominance in the prevalence of both reported drug allergy and immunologically-mediated drug allergy.¹³⁻¹⁷

Specific Drugs and Gender

Large population studies have demonstrated that adult females have higher “allergy” prevalence rates for all classes of drugs.^{6,7} One recent study reviewing drug induced anaphylaxis (DIA) found that penicillins were the most likely culprits followed by sulfonamides and then NSAIDs.⁶

Park et al. specifically addressed female gender as a risk factor for penicillin allergy and found that out of 64 patients with positive penicillin skin testing, 53 were females (83%) and 11 (17%) were males. In this study, females had an odds ratio of 3.2 for positive penicillin testing. When the wheal size increased to 5 mm the gender gap narrowed.¹⁸ This study did not use drug provocation testing to confirm allergy and had a small sample size.

There are five different sub-types in NSAID hypersensitivity which vary based on mechanism and clinical symptoms. These include NSAID exacerbated respiratory disease (AERD), also

called (NERD), NSAID-exacerbated cutaneous disease (NECD), urticaria or angioedema induced by multiple NSAIDs, single NSAID-induced reactions, and delayed NSAID reactions. Data on risk factors for NSAID hypersensitivity is limited but AERD is more common in adult females.^{19,20} One recent study reviewing reactions to prescription NSAIDs using the electronic medical record and informatics in a large health care system reported that adult females have a 1.8 odds ratio for NSAID hypersensitivity reactions.²¹ It is unclear if gender is a risk factor for children with NSAID allergy and this may vary depending on the sub-type.^{22,23}

There are reports of female predominance in cases of reactions to radiocontrast media, peri-operative anaphylaxis, anesthetics and anti-epileptic drug reactions, although large scale studies are lacking. Traditionally, radiocontrast media allergy was considered to be a female predominant condition with some studies reporting that females had up to 22 times the risk to develop the pseudo-allergic reaction, driven by non-IgE mediated mast cell degranulation, compared to men. A theory of the predominance was related to females having a higher dose per body weight and may have been influenced by the use of high osmolality dye.²⁴ However in one study, there was no gender difference but females appeared to be more vulnerable to serious reactions.⁴ Another study from 2012 reports a total of 0.5% of females versus 0.3% of males had a radiocontrast agent “allergy.”²⁵

One interesting study compared the frequency of developing rash with antiepileptics in females to males. The authors reviewed a total of 663 patients with 2,567 exposures to 15 different antiepileptics, and reported that rash frequency was higher in females during the reproductive years compared to men in the same phase of life.²⁶

Drug allergy is more commonly reported in adult females than males but this same discrepancy does not occur in children. It is possible this is secondary to increasing use of antibiotics as one ages, but additionally, females may have a higher propensity for immunologically-mediated drug reactions due to the biological differences between males and females that surface after puberty. To understand how the female gender may be a risk factor for drug allergy, one has to delve into male and female genetics, primarily related to the X chromosome as well as hormones throughout their life cycles.

Epigenetics and the X Chromosome

Male and female sex differences start with the differential in genetic material found in the X and Y chromosome. The process of genetic dose equivalency is dependent upon epigenetic modification. Epigenetics is the study of heritable changes in gene function that are unrelated to the gene itself. DNA methylation, posttranslational histone modifications, nucleosome occupancy, and small and long non-coding RNAs modify the DNA by promoting or suppressing accessibility to particular regions of the genome. This process changes transcription of the gene without altering the nucleotide sequence and leads to altered expression of the gene. These epigenetic modifications may influence an individual's predisposition to develop certain disease states and may contribute to the varied expression of the immune response and allergic expression throughout life.²⁷

Females are functional mosaics for X-linked genes due to the epigenetic process involving the noncoding RNA X inactivation specific transcript (XIST) which mediates X chromosome inactivation (XCI). In most cases, XCI occurs randomly early in development to balance X-linked gene products between males and females (figure 1). Nonrandom or skewed XCI occurs

when there is a preference for one X chromosome to be silenced, such as in mutations or in a stochastic event. Skewing of the X chromosome is defined as 75% or more cells being skewed toward the preferential X chromosome and extreme skewing occurs when >90% retain the same X chromosome. Inactivation will fail in at least 10-15% of female genes, leading to expression of both X chromosomes due to escape of the X chromosome from XCI.²⁸ Over 16% of females over the age of 50 have evidence of skewed XCI, resulting in the preferential expression of one X chromosome over the other. Typically this does not result in disease however; extremely skewed XCI has been demonstrated in some autoimmune diseases and immune deficiency states. Skewing of XCI can also occur over time as one parentally derived X chromosome leads to selective cell death due to problems with maintaining XCI.²⁹

This could explain why autoimmune diseases tend to present later in life and be progressive. We know that epigenetic modifications can also mediate the effects of the environment on allergic disease and immune response.^{30,27} Chemicals and drugs can act on epigenetic controls of gene expression in SLE.^{31,32} Anaphylaxis to medications are more common in females and older individuals, often attributed to more exposure to medications, however it is possible that their vulnerability to develop immune responses to medications changes with age.^{6,13,33-37} Currently, there are no significant laboratory studies that have investigated differing epigenetic regulation by sex in drug allergy. Epigenetics might be one part of the puzzle that explains the high degree of variability in gender specific immune responses throughout life, however sex hormones are also known to modify female response in immune and atopic conditions which fluctuates with reproductive status.

Female Predisposition to Disease

Males tend to have a less efficient humoral immune response which is supported by higher rates of parasitic infections and lower rates of antibody response to vaccines.³⁸ Females are more susceptible to autoimmune diseases including multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis, resulting from a more vigorous immune response. Sex hormones are known to play a crucial role in an individual's immunity and directly influence both allergic, inflammatory cells and their functions.³⁹ Females have cyclical expressions of allergic and asthmatic responses which vary depending on menstruation, pregnancy, and menopause. For instance, one study showed a significant increase in the size of the wheal-and-flare response to histamine on days 12-16 of the cycle, corresponding to ovulation and peak estrogen levels in both atopic and non-atopic females.⁴⁰ In addition, peri-menstrual asthma is common in females and is associated with more severe disease.⁴¹

Most studies on sex hormones focus on their influence on asthma variation in females, likely fueled by the striking gender effect on quality of life and cost of healthcare. Females over the age of 25 account for >62% of hospitalizations for acute asthma exacerbations and are more likely to be corticosteroid resistant.^{2,42,43} In infancy, males have an increase in wheeze and albuterol use which was traditionally attributed to smaller airways relative to lung volume compared to females. However, by young adulthood, females have more small airway resistance and decline in FEV1 compared to males.⁴⁴ In addition, early menarche (<11 years) in girls is associated with increased risk of new-onset asthma compared with typical onset of menarche (11-13 years).⁴⁵ In a recent meta-analysis, irregular menstruation was associated with current atopic asthma with an odds ratio of 2.57 (95% CI, 1.66-3.98), but not with current non-atopic asthma.⁴⁶ These clinical findings are supported by laboratory studies that demonstrate the differential effect that male and female hormones impart upon immune cells in the development

and expression of asthma and allergy.^{2,47} Many asthmatic females have improvement of symptoms in pregnancy. However, females that have worsening of symptoms tend to have more severe asthma and typically improve within 3 months postpartum. Oral contraceptive use for asthma control has been studied and is conflicting. Some studies have concluded worsening of asthma and wheezing while on contraceptives, but other studies have noted a reduction in the number of acute care visits and physician diagnosed wheezing. Menopause and hormone replacement may also influence first time wheeze in a female or lead to drastic improvements in asthma symptoms in others.²

Female Predisposition to Anaphylaxis

Anaphylaxis by all causes is reported more frequently in adult females than males. This difference surfaces after puberty, suggesting that sex hormones may be involved.^{48,49} In addition, cases of catamenial anaphylaxis have been reported, further implicating estrogen or progesterone as potential triggers.⁵⁰ A mouse model by Hox et al may support the concept of estrogen's effect on anaphylaxis. Ovariectomy resulted in reduced severity of anaphylaxis in a mouse model. Subsequent estradiol supplementation of the same mice restored the severity of the anaphylactic reactions. Interestingly, these ovariectomized animals had similar serum concentrations of mast cell mediators compared to the nonovariectomized (hormonally intact) animals, indicating that the estrogen effect was not augmenting the IgE response. However, increased vascular permeability and higher expression of endothelial nitric oxide synthase (eNOS) was found in the female mice compared to the male mice. Their data provides experimental evidence that estradiol may upregulate eNOS expression resulting in the production of NO which is critical for increased vascular permeability and severe anaphylaxis.^{50,51} This murine study prompted a group to review the European Anaphylaxis registry⁵² and stratify data

according to severity and divide them based on age and gender. They reviewed a cohort of 5765 patients (2792 males and 2973 females) and determined that the prevalence of anaphylaxis in adults is higher in females, however the opposite picture evolves concerning severity of anaphylaxis.⁵³ Supporting these findings, a recent study by Jerschow in the United States reviewed diagnostic codes related to cause of death from 1999-2010, and found there was no significant difference in rates of fatal anaphylaxis between genders.¹¹ At this point, it is unclear if the murine data is applicable to human experiences of anaphylaxis but may be a starting point for further investigations.

Drug Induced Anaphylaxis and Gender

Drug Induced Anaphylaxis (DIA) has followed this same trend, with anaphylaxis to drugs reported more frequently among adult females.^{6,13,17,33-37} Over the past five years, more studies focusing specifically on drug-induced anaphylaxis in various countries have surfaced (Table 1). One recent large study examined the electronic records of all patients who visited two hospitals in Boston between 1995 and 2013. It gathered information regarding their drug allergy status and history of DIA. Out of the 1,756,481 patients, 1,017,343 (57.9%) were female. 19,836 reported DIA and 14,668 (73.9%) of this latter group were female. In this study female gender had an odds ratio of 2.20 (95% CI 2.13-2.28) for reporting of DIA. There was also an association between predominantly female conditions with the risk for DIA, including Sjogren's syndrome, asthma, endometriosis, Systemic lupus Erythematosus, rheumatoid arthritis, multiple sclerosis, and thyroid disease.⁶

There is no clear gender predominance in children with DIA. One group from Canada recently recognized a disparity in gender related to DIA. This was an observational study which collected

data on children and adults either retrospectively or prospectively from June 2012 to May 2016. In this study only 18/64 (28.1%) of adults with anaphylaxis were male while 27/51 of the children who had anaphylaxis were males (52.9%) so they concluded that while there is no gender disparity in children with DIA, fewer episodes of DIA occur in male adults.¹³ Another study evaluated 561 children and adolescents for drug allergy using a standardized anaphylaxis scale, skin testing and/or drug provocation. Out of the 561 individuals referred for possible DIA, only 113(19%) were suspected to have immunologically-mediated DIA based on clinical history. With further evaluation including skin testing and/or drug provocation testing, only 84/ 561 (15%) were confirmed to have true DIA. Interestingly, the majority of reactions (66%) in boys occurred when they were <12 years of age.¹⁴

Female predominance after puberty has also been demonstrated in vaccine-induced anaphylaxis. In a large study examining a total 25,173,965 vaccine doses, although anaphylaxis to vaccines was noted to be rare, it was interesting that children who experienced anaphylaxis were predominantly male whereas adults were predominantly female.⁵⁴

Sex Hormones and Allergic Disease

If female risk for immunologically-mediated drug allergy and DIA increases with age, it is possible that male and female hormones play a role in this risk. Sex hormones are known to play a crucial role in an individual's immunity and directly influence both allergic, inflammatory cells and their functions. These hormones promote gene expression or activate/ inhibit signaling transduction after binding to cell surface receptors on a wide array of cells types throughout the body. The main female hormones are estrogen and progesterone while the main male hormone is testosterone. In general estrogen induces a more vigorous immune response, whereas

androgens and progesterone tend to be inhibitory and mount a less efficient immune response.³⁹

Their role in the adaptive and innate mechanisms that drive allergy has been well studied, though mainly in laboratory animals.

Over the last few decades, our understanding of how sex hormones interact with the adaptive and innate immune system stem mostly from mouse models involving hormone receptor and cellular knockouts, as well as castration and hormone replacement. Most of these studies have focused on the mechanisms behind the complex interactions between estrogen and asthmatic inflammation. These studies provide the experimental evidence that sex hormones interact with integral cells involved in the allergic pathway (table 2). In fact, sex hormone receptors are present on virtually every cell in the body making it possible for them to influence immune reactions. There are two main categories of estrogen receptors (ERs): Nuclear and membrane bound G-protein-coupled. Estrogen readily penetrates the cell membrane and triggers dimerization after encountering the ER in the cytosol. Once the ER is freed from the heat shock protein (HSP) 90, it translocates to the nucleus and engages the estrogen response elements (EREs) on target gene promoters. The various ER isoforms and layers of regulatory proteins allow estrogen to interact with transcriptional factors leading to both activation and/or suppression of biological pathways. Similar to estrogen, progesterone also interacts with various cells by signaling through nuclear isoforms and membrane bound receptors but can also signal through a glucocorticoid receptor. Testosterone interacts with the androgen receptor NR3C4.^{39,47,55}

The ubiquitous expression of estrogen, progesterone and testosterone receptors allows sex hormones to affect a wide array of cells in the body inducing an antagonist or synergistic effect that also relies upon dosing of hormones. This results in an array of cellular responses with a

high degree of diversity allowing sex hormones to directly affect interactions between dendritic cells, lymphocytes, mast cells, basophils and eosinophils which are essential in both adaptive and innate immune responses.^{39,47}

Adaptive Immunity and Sex hormones

Adaptive immune mechanisms in drug allergy are driven by B and T lymphocytes and the production of an IgE antibody specific for the drug. Although hormonal influence has not been specifically studied in drug allergy, lymphocyte response and antibody production is known to be influenced by hormones in laboratory studies. Both estrogen and testosterone affect Th1/ Th2 balance which varies depending on concentration. For example, low doses of estrogen tip the response towards induction of Th1 cells. However during the luteal phase of menstruation and pregnancy, estrogen may promote Th2 cells, which are necessary in eliciting IgE mediated allergic reactions that may result in DIA. In contrast, testosterone can both dampen Th1 activation by inhibiting IL-12 activated STAT4, and promote Th2 activation leading to poor clearance of parasitic infections. Testosterone has also been shown to decrease IgE production from B cells following allergen challenge.⁵⁶ Laboratory studies have demonstrated that estrogen enhances histamine release from rat mast cells and sensitized human basophils upon stimulation with anti-IgE.^{57,58} Sex hormones are known to interact with dendritic cells (DC), lymphocytes, eosinophils and basophils sometimes in a cyclical dose dependent manner that can result in the development, augmentation, or suppression of IgE mediated response (table 2).^{2,39,55-57,59-73}

Innate Immunity and Sex Hormones

In addition to gender specific response in adaptive immunity, there is evidence that the innate immune system is expressed differently in males and females. Recent studies in mice have

shown that testosterone and androgen receptor signaling reduce type 2 allergen induced cytokine proliferation due to not only Th2 and Th17 cells, but also to group 2 innate lymphoid cells (ILC), which are integral in innate immunity and inducing allergic response.^{72,73} Testosterone and progesterone are also known to be potent inducers of T-regulatory cells which play a central role in preventing the expression of allergic symptoms.^{55,68}

Testosterone and progesterone may also dampen allergic responses by inhibiting mast cell mediator release.^{57,58,65} It is possible that the relative number of estrogen and progesterone receptors on mast cells may fluctuate with menstruation or ovulation, leading to either augmentation or inhibition of mast cell mediators.⁶⁵ Estradiol has been shown to augment mast cell secretion when it is inhibited by tamoxifen, an ER antagonist. Estradiol at physiologic concentrations promotes synthesis of mast cell mediators and mast cell degranulation via the ER.⁶⁸

Innate immune receptors such as toll-like receptors (TLR) detect danger signals in the mucosal environment and aid in the interpretation of allergen exposure. It is known that TLR7 is expressed on the X chromosome and promotes stronger anti-viral responses in females versus males. This suggests that sex hormones may modify the perception of danger signals and viral response that could be in play in non-immediate drug hypersensitivity. Alternatively, sex hormones could potentially augment IgE response to a drug or even act as a hapten, promoting sensitization in immediate drug hypersensitivity.³⁹

Conclusion

Drug allergy and DIA are more common in adult females and this propensity develops after puberty. Adult females seek out medical care more frequently and take more antibiotics;

291 however, it is likely that complex interactions of the X chromosome, epigenetics, and sex
292 hormones also drive this gender discrepancy. Yet, there are few studies examining these
293 interactions, specifically in anaphylaxis and drug allergy. When sex differences surface in a
294 condition, researchers should strive to understand the mechanisms behind the sex-biasing factors,
295 as part of a strategy for prevention of disease and identifying new targets for treatment.

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Figure 1 Legend. Xist which is located on the long arm of the X chromosome, mediates X inactivation which drives dose compensation. Typically this process is random (A), however when one X is preferentially expressed, it leads to skewing of X inactivation (B).

Table 1. Summary of recent studies examining Drug Induced Anaphylaxis

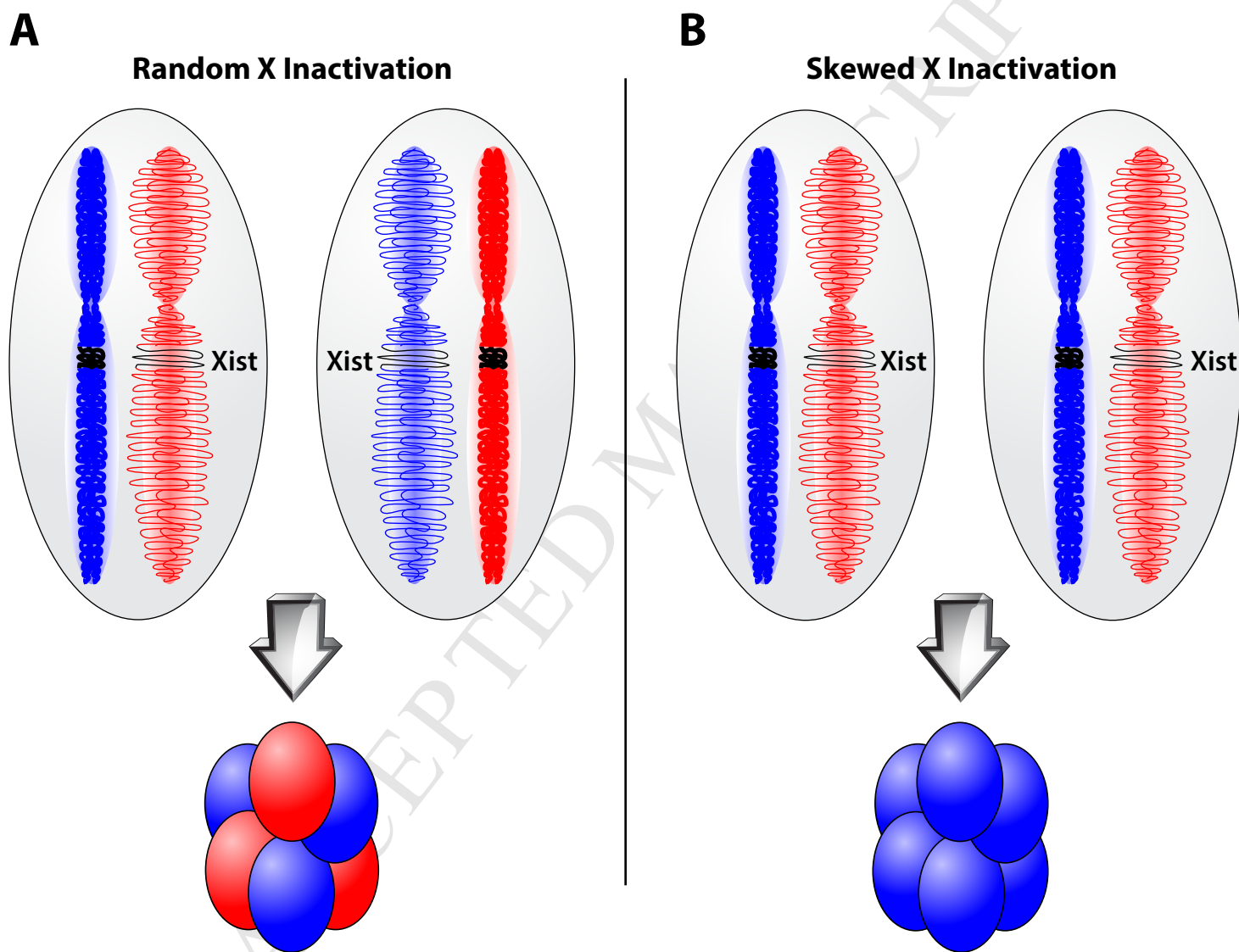
Study	Total number of patients	Total number of patients with actual DIA	Methods/ Database	Mean Age	Years	Drug induced anaphylaxis in females	Drugs	Country
Aun (2014) ¹⁷	806	117/806 (14.5%)	Observational study Skin Testing In vitro tests DPT	38.6+/- 14.5 years(2-70)	January 2006-June 2012	95/117 (81%)	NSAIDS Latex Anesthetics Antibiotics	Brazil
Banerji (2014) ³³	716	716	Observational study Medicare Database using ICD codes	48+/- 19 years(0-65)	2002-2008	508/716 (71%)	Not identified	United States
Cavkaytar (2017) ¹⁴	561	84/561 (15%)	Observational study Skin testing DPT	Children and adolescents: 9.6 years(5.4-13.8)	January 2012-February 2016	37/84(44%)	Antibiotics NSAIDs Chemotherapeutics Others	Turkey
Dhopeswarkar (2018) ⁶	1,756,481	19,836 (1.1%)	Observational study Electronic Health Record: Partners	Adults	1995-2013	14,668/19,836 (73.9%)	Penicillins, sulfonamides, and NSAIDS	United States
Faria (2014) ³⁴	313	313	Observational study National Anaphylaxis Notification System	43.8 (2-89)	January 2007-December 2010	207/313 (66%)	NSAIDS Antibiotics Anesthetic agents	Portugal
Gabrielli (2018) ¹³	64 adults 51 children	64 adults 51 children	Observational Study Cross-Canada Anaphylaxis Registry	Adults: 48.9 Children: 8.95	June 2012-May 2016	Adults: 46/64 (72%) Children: 24/51(47%)	Antibiotics NSAIDS Radiocontrast Other	Canada
Jares (2015) ³⁶	1005	264/1005 (26.3%)	Observational study Database encompassing 11 Latin American Countries	38.2 (1-84)	December 2011-July 2014	Adults: 159/215 (73%) Children: 21/49 (42.9%)	NSAIDS Antibiotics Corticosteroids Neurologic Drugs Local Anesthetics Others	Latin America
Renaudin (2013) ³⁷	300 adults 33 children	300 adults 33 children	Observational study Skin testing In vitro tests DPT	Adults: 46.4+/- 14.6 years Children: 9.8 +/-4.5 years	2002-2010	206/333 (61/9%)	Antibiotics Muscle relaxants Latex Anesthetics Contrast NSAIDS Others	France
Zhao (2017) ³⁵	9425	1189/9425 (13%)	Observational study Beijing Center for ADR monitoring	47.6+/- 20.1	January 2004-December 2014	627/1189 (52.7%)	Antibiotics Traditional Chinese Drugs Radiocontrast Antineoplastic Agents	China

Total number of patients (column 1) varies from study to study and can represent either the total population or the total number of patients with suspected drug allergy or drug induced anaphylaxis

Table 2. State of current experimental data supporting hormonal interaction with allergic and inflammatory cells

	Dendritic Cells	B Lymphocytes	T Lymphocytes	Mast Cells	Eosinophils/ Basophils
Estrogen	-Enhances DC sub-populations ⁵⁹ -Stimulates DC driven Th2 response(<i>human tissue</i>) ⁶⁰	-Promotes B cell expansion and lowers threshold for B cell activation -Negatively impacts B cell tolerance ³⁹	-Effects on T cell activation and Th1/Th2 balance(<i>animal and human tissue</i>) ³⁹ -Combined with progesterone, increases Th17 differentiation and IL-17A production ²	-Induces synthesis of mast cell mediators and degranulation ⁵⁷	-Induces eosinophilic inflammation in the peripheral blood and BAL fluid ⁶¹
Progesterone	-Inhibits DC activation -Reduces DCs ability to activate CD4+T cell proliferation ⁶²	-Influences B cell function ³⁹ -Increases IL-10- producing B regulatory cells which prevents mast cell activation in the airways ⁶³	-Potent inducer of Treg cells(<i>animal models and human cord blood</i>) ⁵⁵ -Suppresses T cell dependent antibody responses ⁶⁴	-Suppresses histamine secretion from purified rat peritoneal mast cells ⁶⁵	-Enhances eosinophil degranulation in mice ⁶⁶ -Combined with estrogen promotes human eosinophil degranulation(<i>human tissues</i>) ⁶⁷
Testosterone	-Inhibits DC activation, cytokine production and immune response(<i>animal and human studies</i>) ⁶⁸	-Inhibits B cell maturation and antibody production ⁶⁹ - Decreases IgE production from B cells following allergen challenge ⁵⁶	-Can affect T cells both directly and indirectly via differentiation, induction of Tregs and regulation of T-dependent antibody response ⁶⁸ - Decreases allergen-induced IL-5 and IL-13 production from Th2 cells, ILCs and IL-17A production from Th17 cells ⁵⁶	-Suppresses histamine secretion from mast cells ⁶⁵	-One study demonstrated that it does not influence IL-4 generation in basophils (<i>human basophils</i>) ⁷¹ -Decreases eosinophilic inflammation to allergen exposure ^{56,72,73}

Abbreviations: Dendritic Cell (DC), Bronchoalveolar Lavage (BAL), T-regulatory Cells (Tregs), Innate Lymphoid Cells (ILCs). *All of these studies were performed in laboratory animal or tissue models with the exception of those noted.



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Key Messages

Females are more likely to have asthma and atopic conditions throughout their lives, which are cyclically affected by their reproductive status.

There is experimental evidence to support sex hormones roles in the allergic and inflammatory response.

Drug allergy and drug induced anaphylaxis is more common in adult females compared to males and this propensity develops after puberty.

Although drug induced anaphylaxis is more prevalent in adult females, fatal or severe drug induced anaphylaxis is not.

Disproportionate utilization of healthcare, genetic factors related to the X chromosome, epigenetic changes, and discrepant hormonal interactions with immune cells contribute to the gender discrepancy in drug allergy.