



Drug allergy management in the elderly

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Purpose of review

Drug allergy management has previously not been emphasized in the elderly. However, the geriatric population poses several unique characteristics, challenges for drug allergy testing and considerations in the management. Especially in the era of COVID-19, the elderly population is a vulnerable cohort and reviewing the management during this unprecedented time is both timely and relevant.

Recent findings

In recent years, larger scale studies focusing on the epidemiology and prevalence trends of drug allergies among older adults has been summarized in this review. Emphasis on anaphylaxis in the older adults has been studied.

Summary

There are many implications of these findings. Epidemiological studies are useful in realizing the burden and spectrum of drug allergies on our healthcare system. It has allowed us to identify certain barriers in drug allergy management and develop ways to overcome these challenges through. Lastly, we have proposed an approach to drug allergy management based on previous studies as well as from our perspective and local experience.

Keywords

COVID-19, drug allergy, drug hypersensitivity, elderly, older adults

INTRODUCTION

Population aging is a global phenomenon with an estimate of over 720 million aged 65 years and older worldwide, with trends in Asia even surpassing those of European countries in the past decade [1,2]. Drug allergy in this growing population can have adverse consequences, especially in this vulnerable population. We know that most drug allergy labels, especially beta lactam antibiotics, after thorough drug allergy workup are not true allergies [3,4,5]. It has also been shown that delabelling initiatives, especially penicillin allergies, to be cost effective. However, many of these studies do not focus on the impact and barriers of drug allergy workup in the elderly population (age $\geq$ 65 years old). Although data is sparse regarding drug allergy management in this population, this article focuses on the prevalence, risk factors, obstacles and barriers to drug allergy management and offers guidance for managing drug allergy in the elderly.

EPIDEMIOLOGY

The spectrum and causes for drug allergy invariably differ in the elderly population. Up to 30% of adverse drug reactions in the elderly on retrospective evaluation were hypersensitivity reactions [6].

Among hospitalized patients, the prevalence of drug allergies among the elderly is even higher. Of the 492 patients with drug allergy labels, 69.3% were over 65 [7]. Various factors distinguishing drug allergies among the elderly include drug exposure and sensitization, comorbidities, educational level, and genetic and ethnic predisposition [8]. Regional factors such as availability of different drug formulations, standard practices of drug use, antibiotic stewardship programmes will also affect the spectrum of drug allergy. In a recent study looking at piperacillin-tazobactam allergy, it was found the increasing rate of allergy to this broad-spectrum antibiotic correlated with increased prescription [9]. Among inpatients from a single tertiary centre in Hong Kong, significantly more patients in the geriatric group had drug allergy to cardiovascular system drugs (15.5% vs 4.6%, $P = 0.001$) [7]. Antibiotics and

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Curr Opin Allergy Clin Immunol 2021, 20:000–000

DOI:10.1097/ACI.0000000000000761

KEY POINTS

- There needs to be greater emphasis on drug allergy management in the elderly as this population pose unique clinically characteristics, prevalence and risk factors
- We have identified several barriers and obstacles to drug allergy management including patient and physician factors and factors associated with the healthcare system.
- There are several factors we need to consider when managing drug allergies among the elderly, especially in the COVID era.

nonsteroidal anti-inflammatory drugs were still the top two classes of drugs responsible labelled drug allergies [7]. In a large prospective, cross sectional study of elective surgical patients, a large proportion were elderly with 20% over 75 years old and 46.4% falling between the 51–75 age group category [10].

RISK FACTORS FOR DRUG ALLERGY IN THE ELDERLY

There are various risk factors associated with the development of drug allergy labels in the elderly. In a retrospective study, the presence of concomitant comorbidities in those age > 65 was 100% compared to 9.23% ($\chi^2=0.00$) in those under 65 years old [6], whereas presence of allergic diseases and family history of atopy seem to be a significant risk factor in the younger population (3.69% vs 24.61%, $\chi^2=0.00$, and 0 vs 6.1%, $\chi^2=0.005$, respectively). Comorbidities invariably lead to increased drug exposure and sensitization leading to the developing drug allergies. Polypharmacy is a well-known problem amongst the elderly and multiple drug regimens is a risk factor in the elderly (86.5% vs. 30.7%, $\chi^2=0.00$) [6,11,12]. There is increased use of antibiotics among elderly homes, with risk factors including increasing age and presence of certain comorbidities such as chronic respiratory disease, urinary tract infections and skin and soft tissue infections [13]. Other risk factors include chronic renal insufficiency and concomitant treatment with beta-blockers and thiazide diuretics.

ADVERSE EFFECTS OF DRUG LABELS

Adverse consequences among patients carrying a drug allergy have been well documented especially for beta-lactam antibiotics [14]. In a study among US veterans, with a mean age of 70 years old, there were statistically less adverse drug events (2 vs 12%,

$P<0.005$) and ESBL organisms (1 vs 6%, $P=0.06$) using preferred compared with nonpreferred antibiotics [15].

ANAPHYLAXIS IN THE ELDERLY

Drugs remain the second most common cause of anaphylaxis among adults after insect venom, with food-related anaphylaxis coming in third contrary to the paediatric population [16,17]. Certain drugs used more among elderly, such as beta-adrenoceptor antagonists and angiotensin converting enzyme inhibitors, increase the risk of anaphylaxis. Age is a major risk factor for the development of severe anaphylaxis (OR 1.020, 95% CI 1.002–1.039, $P=0.033$) [18]. Each year of advancing age is associated with 1.6% (CI 1.4–1.9%) increase in the odds of experiencing a severe anaphylactic event, even after adjusting to other confounding variables [19]. Most guidelines do not recommend the routine administration of adrenaline autoinjectors for drug-related anaphylaxis when the culprit has been correctly identified [20]. However, only 15% of adult patients indicated for prescription of adrenaline autoinjectors were given prescription, which was also significantly less compared to the paediatric population (36.5% vs 89.4%, $P<0.001$) prompting the need for a regional consensus statement [21²²].

There is often increased resistance in using adrenaline for the management in anaphylactic patients with underlying cardiovascular disease. In a retrospective study of 296 patients, patients aged 80–89 years old had greater odds of experiencing an adverse cardiac effect compared with those between 50 and 59 years old (OR 8.8; 95% CI, 1.2–67.1) [23]. A large European Anaphylaxis registry observed that among their 1123 elderly anaphylactics, they were less likely to present with skin symptoms ($P<0.001$) and more likely to present with loss of consciousness (33%, $P<0.001$). Cardiovascular comorbidities were significantly higher among the elderly (59%, $P<0.0012$). Adrenaline was used only in 30% of elderly vs 26% of younger adults ($P=0.043$) and older adults were more statistically likely to be hospitalized (60% vs 50%, $P<0.001$) [17]. Drug, such as angiotensin converting enzyme, beta-blockers and proton pump inhibitors were more significant in the elderly (57% vs 18%, $P<0.001$) [17]. There was a significantly higher rate of contrast allergy (8% vs 4%, $P=0.01$) and analgesics in the elderly. Rate of antibiotics, analgesics, local anaesthesia, proton pump inhibitors and cardiovascular drugs were similar. In another retrospective analysis, analgesics allergies were more significant in the elderly (RR 1.57, RR 1.46–1.7, $P<0.001$) [24]. Other drugs such as contrast, antibacterial and anti-inflammatory

drugs suggested a lower risk in the elderly. However, it is important to note that there were no penicillin-based antibiotics except for piperacillin which may signify different practices or patient selection in that particular tertiary centre. A large-scale retrospective study carried out in New York found that anaphylaxis rates among the elderly increased over a span of 10 years [25^{***}].

DRUG ALLERGY TO SPECIFIC DRUG GROUPS

Literature regarding drug allergy to specific groups of drugs remain sparse among the elderly. In our local data, the proportional prevalence of the top ten drug groups among the geriatric and nongeriatric group is similar except for cardiovascular drugs as forementioned.

Beta-lactams continue to be the leading cause of drug allergy in both populations, followed by non-beta-lactam antibiotics, nonsteroidal anti-inflammatory drugs and radiocontrast [7]. In a prospective study looking at 565 elderly patients, anaphylaxis, side-chain reactions and a positive drug challenge were more frequent in those within the 60–79 year bracket compared with patients over 80 years old [26]. There were more benzylpenicillin, amoxicillin and ceftriaxone sensitizers in the over 80 years old group ($P < 0.01$). There was also less urticaria symptoms reported and more unknown clinical history. Skin test positive for amoxicillin (72.2% vs 16.6%, $P = 0.002$) and positive amoxicillin reaction on basophil activation test (23.8% vs 0% $P = 0.025$) was more significant in adults than children.

In patients with contrast allergy, history recall was unreliable. After workup with drug provocation test, 95.9% of patients could tolerate either the culprit or alternative contrast medication. The negative predictive value for skin tests was 96.2% for immediate-type reactions and 58.8% for delayed-type reactions ($P < 0.0001$, Fisher's exact test) [27].

Serious allergic reactions with pyrazinamide allergy were independently associated with older age (OR 1.013; 95% CI 1.004–1.023; $P = 0.007$) after sex and underlying comorbidities were adjusted [28]. On the contrary, anaesthetic anaphylaxis was less common among elderly (OR 0.71 (CI 0.61, 0.83) $P < 0.0001$ [8].

BARRIERS TO DRUG ALLERGY MANAGEMENT IN THE ELDERLY

Many barriers exist for optimal management of drug allergy among the elderly including both patient and physician factors.

Physician factors

Several factors have been identified including lack of resources and time from nonallergists, fear of provoking an anaphylaxis, inability to recognize and manage anaphylaxis in a timely manner and a lack of initiative due to low priority [29]. In Hong Kong particularly, the lack of allergists is also a major barrier to timely management of drug allergies [30]. Allergy testing also relies on the timely referral by physicians, pharmacists and other healthcare providers. Lack of knowledge and need for drug allergy management, the availability of drug allergy centres and being unaware of guidelines and referral pathways are a few factors that pose the greatest obstacles in tackling drug allergies in the elderly [10].

Patient factors

Through multivariable analysis, the effect age had on whether the patient had the motivation to be tested was significant. Those over 75 yr age range less likely to want testing (OR 0.34, CI 0.2–0.55, $P < 0.01$) [10]. Many elderly patients cannot accurately give a good history. Cognitive decline is also a major factor determining the ability for allergists to proceed with a well-consented procedure. Frail elderly with impaired mobility would also pose a physical challenge for both patients and carers to be seen at an allergy centre for testing, especially in patients with multiple drugs requiring multiple clinic attendances.

Factors associated with the healthcare system

In Hong Kong, we have a centralized electronic system within the public sector with a drug allergy alert system that is physician reported. Phone apps are also available for doctors in the private sector to view these records although the reverse is not available. In one study highlighting the inconsistency of drug labels in the medical records, there was no description of the sensitivity in 81% of cases and only 2/48 hypersensitivity reactions were simultaneously recorded in the administration, care home and general practitioner's record [31]. In one large retrospective study, relying on ICD-9 codes alone missed approximately half of the cases of anaphylaxis [25^{***}].

OVERCOMING BARRIERS TO DRUG ALLERGY MANAGEMENT

Improve awareness and education for drug allergy assessment and management amongst frontline healthcare workers (physicians, nurses, pharmacists,

etc.) This will improve knowledge for assessment of drug allergies, documenting an accurate drug allergies history and identifying culprits and increase referrals for proper assessment and management by an allergist if needed. Liaising with physicians, pharmacist, and nurses can help improve and utilize referral pathways more effectively.

Implement strategies to improve detection of drug allergy labels among elderly. A centralized electronic system can be utilized to improve documentation and visibility of known drug allergies across different hospitals and regions. Allergy alert cards are crucial in localities without centralized computer systems. In the age of telemedicine, phone health applications can be a great tool to improve communication and also give patients autonomy in their own allergies [32,33]. Elderly living in nursing homes can benefit from a residential care pharmacist to ensure and audit correct drug allergy documentation. We should also stress that delabelling is equally important.

Pharmacist-driven penicillin skin testing and delabelling programmes have been shown to be effective in removing labels, switching to first line antibiotics, reducing length of stay, and antimicrobial costs [34,35]. It has also been shown to be safe and accurate even among the elderly [36]

OVERALL APPROACH TO THE DIAGNOSIS AND MANAGEMENT OF DRUG ALLERGY

Factors to consider in managing drug allergy in the elderly

Not all drug allergy labels are equal

In the geriatric population there are several questions we must ask ourselves. First, do we need to test the drug? Is the drug important or necessary for the patient or would testing prove futile with better alternatives available. We prioritize certain populations who are more vulnerable. For example, we advocate to prioritize first line antibiotic testing for all patients with predisposing medical conditions that can increase the risk of infections. On the contrary, second- or third-line antibiotics should be weighed with the risk and benefits of performing a test. Other drug classes that should be prioritized include chemotherapy, contrast and perioperative medications depending on the history.

What are the considerations during workup in the elderly?

Drug provocation test is gold standard for confirming a genuine drug allergy. In some cases, auxiliary tests such as skin tests and certain *in vitro* tests can

help reduce the risk of direct oral challenge. Certain medications such as beta lactam antibiotics have validated skin test concentrations, although we note that validation is performed in healthy volunteers and the sensitivity and specificity of tests in the elderly are unknown [37].

How safe is drug provocation tests in the elderly?

Given the benefits of delabelling certain drug allergies such as beta lactam antibiotics, we do advocate for all patients with a low risk of drug allergy to undergo complete drug allergy workup. For antibiotics, patients should be advised to complete drug allergy workup and avoid performing auxiliary tests only to avoid a false sense of security. Studies have shown that direct oral amoxicillin challenges for low risk penicillin allergies are safe even in the elderly population [38].

Are there any relative or absolute contraindications to the test?

First, is the patient able to consent to the test (health literacy)? If not, we need to consider alternative medications. On the contrary, elderly with good cognitive function should be not deprived of the benefits of allergy testing. For example, we previously had a patient who developed drug reaction with hypereosinophilia and systemic symptoms after an orthopaedic surgery. He was labelled with suspected allergy to a multitude of perioperative medications including multiple classes of antibiotics. Had we not undergone complete workup, we would have been unable to identify that the culprit was in fact vancomycin in the bone cement [39]. However, we needed to discuss with the patient in length the indications for testing and the risk of another severe reaction regardless of what the *in vitro* and *in vivo* skin tests indicated. In elderly patients, this conversation may not always be possible, and the risks may outweigh the benefits if our patients cannot comprehend completely. Second, poor skin conditions are prevalent among the elderly and this can affect interpretation of skin tests. Third, patients who are physically unstable should not proceed to tests.

Should there be an age limit for drug allergy testing?

No. We feel that age alone should not be a contraindication for tests.

Do desensitization protocols have a role in the elderly?

There is sparse evidence looking at the benefits and risk of desensitization of medications in the elderly

population. One study mentioned the role of allopurinol desensitization protocols. Published desensitization protocols last between 16 and 78 days. However, authors point that long desensitization protocols should be recommended for elderly [40].

Resource availability, cost effectiveness and prioritization

Resources such as expertise, manpower, equipment and cost will determine the ability for healthcare workers to effectively implement drug allergy referrals, assessment, management and subsequent follow up. Prioritizing certain cohorts will be helpful in triaging and reducing the burden of drug allergy management in a territory wide health structure.

DRUG ALLERGY MANAGEMENT IN THE ERA OF COVID-19

The COVID-19 global pandemic has challenged physicians with the responsibility of assessing the patient's needs with public health considerations [41]. It has inevitably changed the way we prioritize and practice allergy medicine today. Old age has been associated with poorer outcomes with COVID-19 [42]. Most guidelines do not recommend routine investigations. Drug provocation tests are not recommended unless there is an urgent need (for example, chemotherapy, contrast and perioperative medications) [43]. Current local and international guidelines for COVID-19 vaccinations recommend to prioritize high-risk patients such as the elderly [44,45]. Patients with multiple drug allergies and history of anaphylaxis, idiopathic anaphylaxis or allergy to previous COVID-19 vaccine, should be referred to an allergist for risk assessment for safe administration of COVID-19.

FUTURE DIRECTIONS

There are several issues that need to be addressed in future research. More elderly focused epidemiology is important to review the bulk of the disease burden and dictate future directions for drug allergy management. Studies are also needed to validate skin tests and drug challenges among elderly patients. Developing *in vitro* tests will become increasingly important especially for patients who cannot consent to or with a high risk of drug challenges. Studies are needed to highlight barrier to drug allergy testing from both the physician and patient point of view. Studying the impact of inappropriate drug allergy labels other than antibiotics will be useful in determining the urgency or need for management.

CONCLUSION

There are unique considerations when assessing the management of drug allergies among the elderly population. Many factors are associated with developing drug allergies in the elderly. Management of drug allergies require a comprehensive discussion between physicians, patients, and carers.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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