



The economics of drug allergy

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Purpose of review

As drug allergy research aims to inform clinical practice, implementation of best practices may be influenced by financial resources required to incorporate new interventions and the resulting clinical and economic returns on those resource investments. The present review summarizes new insights into the economics of drug allergy over the past year.

Recent findings

While considering economic implications of recent drug allergy research, many studies have addressed different contextual factors related to the setting, provider, or outcomes. Advances in technology have enabled specialized allergists to support remote settings through telemedicine consultation. Training opportunities and interdisciplinary approaches to address drug allergy challenges have enabled multiple provider types to play a role in screening, diagnosis, and management. Penicillin allergy testing has been a major focus for many institutions, with several studies focused on de-labeling strategies including confirmatory skin testing and direct oral challenges.

Summary

Studies over the past year provide new opportunities for the field of drug allergy research. The focus of current research to capture direct health costs or savings associated with drug allergy interventions demonstrates opportunity for more cost-effective care delivery and opportunity to explore greater benefits to society.

Keywords

cost-effectiveness, drug allergy, economic evaluation

INTRODUCTION

Advances in the diagnosis and management of drug allergy offer opportunities to improve healthcare delivery in a meaningful proportion of clinical encounters, with prevalence estimates for drug hypersensitivity reactions ranging from 10 to 20% of all adverse drug reactions (ADRs) with cutaneous reactions being the most commonly reported [1–3]. Although clinicians and researchers investigate new methods to approaches to address the healthcare burden of drug allergy, decision-making and implementation may be influenced by the financial resources required for new interventions and the economic impact once a change has been implemented. This scoping review aims to highlight recent literature that may provide new insights into the economics of drug allergy.

HEALTHCARE DELIVERY PRACTICES AND OTHER ISSUES

Donabedian [4] described a systems approach of evaluating the quality of healthcare delivery in his seminal paper outlining a structure-process-outcomes framework. Advances in health practices

related to drug allergy may be categorized and described in a similar fashion, as many interventions often develop out of necessity to address contextual factors related to the setting, provider, and outcomes desired.

Importance of allergy evaluation by more provider types

The high prevalence of suspected or reported drug allergy and limited supply of specialized allergists puts a greater demand on the use of drug allergy evaluations by emergency department clinicians, pharmacists, infectious disease specialists, nurses, and general practitioners [5**]. Given the advanced training in pharmacology, pharmacokinetics, pharmacodynamics, and other medication-related

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KEY POINTS

- Training and education may be a limitation for implementation of current drug allergy best practices.
- Developing multiple provider types to support drug allergy practices may address allergist supply challenges.
- Penicillin allergy evaluation has been the focus of much of the economic research in drug allergy over the past year.
- High cost areas such as organ transplant, genomics, and inpatient or emergency services may be areas of interest for cost-savings opportunities.

information, pharmacists have been used frequently in various drug allergy management services developed recently. Jones *et al.* [6[•]] demonstrated that a pharmacist-managed, nursing-performed penicillin skin testing (PST) protocol implemented in a 714-bed community-based regional health system helped de-label patients resulting in better care and reduced costs. Additionally, a pilot-controlled trial of two long-term care residential facilities in Australia found allergy and ADR history was better documented in the facility where a pharmacist was incorporated to perform medication reviews [7].

Appropriate training

In order to expand drug allergy evaluation, investment will be required in appropriate training and education. In the United Kingdom, a survey of non-medical prescribers (nurses, pharmacists, radiologists, and physiotherapists) found that respondents with greater confidence in identifying ADRs were more likely to report the event to the country's adverse event reporting system and that additional training was associated with increased ADR reporting [8]. A recent audit of electronic medical records (EMRs) for 332 patients admitted to general medicine services in a New Zealand hospital found that 46% of patients admitted had a documented drug allergy in their profiles when true hypersensitivity was actually only 20%, demonstrating quality concerns for EMR documentation of ADR reporting [9^{••}]. Further, the Australasian Society of Clinical Immunology and Allergy Drug Allergy Working Party identified multiple deficiencies in drug allergy knowledge and skills of healthcare professionals such as inability to recognize and appropriately manage severe allergic drug reactions, poor communication of known allergies, and misuse of terminology [10[•]].

Telemedicine opportunities

The use of technology and advancement of telemedicine practices have enabled greater access to allergists to evaluate suspected drug allergy cases [11^{••},12]. Staicu *et al.* [11^{••}] demonstrated feasibility and potential cost savings of combined skin testing and telemedicine consultation with a remote allergist through a pilot in 50 patients with suspected penicillin allergy. Using an interdisciplinary approach with a pharmacist obtaining a detailed patient history, a physician assistant performing the skin test, and a real-time video conferencing consultation with the allergist, the investigators found a direct reduction in costs as de-labeling patients resulting in more appropriate, lower costs antibiotic selection [11^{••}]. Phadke *et al.* [12] further demonstrated the potential for electronic consultation as a substitute for in-person consults in the cases of ADR, immunodeficiency, and urticarial/angioedema.

Setting type

The inpatient setting has been a major focus of several interventions, observational studies, and economic evaluations related to drug allergy [6[•],13,14[•],15[•],16]. Similarly, the emergency department (ED) has been utilized to implement and assess strategies to address potential ADRs related to drug allergy [17–19]. These institutional-based settings provide a great opportunity for guideline-focused interventions where clinical staff training can be standardized and many facilities in the United States are already associated with universities. Additionally, interventions that offer even a modest clinical benefit (e.g. 1 day reduced length-of-stay) could potentially offer significant financial savings because of the high custodial costs of hospital care in the United States. Research in ambulatory or outpatient settings has been less frequent, but potential management pathways for antiepileptic drug induced skin reactions could aid outpatient clinicians in early identification of patients at risk for developing severe allergic reactions [20]. In the case of suspected penicillin allergy, Iammatteo *et al.* [21^{••}] demonstrated that oral graded challenges to amoxicillin in the outpatient setting may be well tolerated for patients at least 7 years old with non-life-threatening historical reactions to penicillin.

Penicillin skin testing or not

Specific to patient-reported penicillin allergy, skin testing may not be necessary for confirmation. In a recent review, Shenoy *et al.* recommend prescribing amoxicillin or performing a direct amoxicillin challenge in

low-risk patients where patient histories include non-allergic symptoms or solely a family history of a penicillin allergy based on the availability of multiple oral provocation studies [5^{22,23}]. Shenoy *et al.* [5²⁴] did recommend skin testing and amoxicillin challenge in patients with moderate-risk histories such as urticarial or other reactions suggestive of an IgE-mediated response, but no history of anaphylaxis. Differentiating between an IgE-mediated reaction from late reactions through the patient's history and establishing that the patient is at a low-risk of a life-threatening reaction is important prior to oral challenge. The evidence supporting PST has grown significantly in recent years demonstrating potential for improved health outcomes and cost-savings [6¹¹, 14²⁴]. Direct oral challenge with amoxicillin may be a well tolerated and effective alternative to skin testing for low-risk patients, making a case for a guided approach to evaluation rather than institutions broadly requiring skin testing on all patients [25²⁶].

BIG DATA

In order to provide clinicians with guided approaches to evaluate and manage drug allergies, systems can further leverage existing data to identify patients with increased risks for ADR and implement additional decision-support.

Predictive analytics

One area of focus has been on the pediatric population where antibiotic-related ADRs have been a significant source of avoidable costs [27,28]. Vyles *et al.* [29] provided an allergy questionnaire to 597 parents of children in the pediatric ED, categorized allergy risk based on questionnaire responses, and provided subsequent penicillin allergy testing to 100 of those children defined as low-risk. All 100 low-risk children tested were negative for penicillin allergy were followed with a brief telephone survey to estimate reduced healthcare costs from de-labeling [29,30³¹]. The pediatric population may also be an area for additional drug allergy de-labeling for macrolides, sulfamethoxazole, and other non- β -lactam antibiotics as Grinlington *et al.* [31] found only 18% of challenge tests were positive following further allergy evaluation.

Artificial intelligence methods may further advance the health system's ability to predict and respond to ADRs. Wu *et al.* [32] utilized the Medical Dictionary for Regulatory Activities (MedDRA) and data mining techniques to analyze ADRs in drug labeling documents. Tang *et al.* [33] explored the use of natural language processing algorithms for unstructured (free text) data to detect ADRs in

discharge summaries in a tertiary hospital in Singapore, providing a step toward automated ADR detection from underutilized data sources. Structured data from administrative claims or EMRs also provides a rich source for the advancement of predictive analytics for drug allergy. Saff *et al.* [34] demonstrated opportunities to incorporate multiple diagnosis codes for identification of inpatient allergic drug reactions, which could provide a guide to establishing larger drug allergy cohorts for epidemiological studies.

HIGH COST AREAS

In order to have a major impact on total healthcare spending related to drug allergy, investigators may find the highest return in a few select areas where associated costs are often the highest. For example, Antoon *et al.* [35] evaluated a pediatric cohort with a primary diagnosis of Stevens-Johnson syndrome and toxic epidermal necrolysis across U.S. hospitals and found high adjusted hospital costs (median costs \$16 265) with about 1 in 10 patients readmitted within 30 days of discharge. Multiple researchers have focused efforts on allergy testing in patients specifically receiving aztreonam, a high cost antibiotic, to improve outcomes and reduce costs [16,36³⁷].

Genomics

Genetic testing and genotyping has become another area of development in the evaluation and management of drug allergy patients. Plumpton *et al.* [37] developed a cost-effectiveness analysis of *HLA-B*58:01* genotyping prior to initiating allopurinol for gout to reduce the incidence of hypersensitivity ADRs, but found that routine testing at current prices would not be cost-effective based on thresholds commonly used in the United Kingdom. Ratanavipapong *et al.* [38] conducted a cost-effectiveness analysis of *HLA-B*15:02* genotyping to avoid carbamazepine-induced hypersensitivity ADRs with mixed results demonstrating that universal testing was cost-effective for patients with neuropathic pain but not epilepsy because of the high cost of alternatives for carbamazepine in epilepsy.

Organ transplant

The organ transplant population may be another area where even modest advances in clinical effectiveness could have substantial financial returns. Pryor *et al.* [39⁴⁰] recently explored desensitization with trimethoprim-sulfamethoxazole in solid organ transplant patients with self-reported sulfonamide allergy as an alternative to avoidance. With 80%

(41/52) of organ transplant recipients remaining on a sulfonamide at 3 months with no ADR, the investigators reported a cost-savings of \$575/patient [39²²]. Although this study was based on annual wholesale drug prices (not representative of true payer costs) and a small sample, it does provide a potential area for a more cost-effective approach to care for solid organ transplant patients with reported allergy.

COST-EFFECTIVENESS ANALYSES ISSUES

Cost-effectiveness analysis remains the primary economic evaluation method for health interventions utilized by health economists. With this methodological approach, expert panels convened in 1996 and updated in 2016 have provided a set of recommendations regarding costing, use of quality-adjusted life-years (QALYs) as a primary effectiveness variable for comparison, perspectives, discounting, reporting, and more [40,41].

Which costs?

Cost-of-illness (COI) studies serve to describe costs associated with a particular health state to estimate the economic burden of health problems on a population [42]. By understanding the costs attributable to a given disease, researchers can estimate the value of new interventions over current standards of care. A recent systematic review found for studies focused on penicillin allergy, several types of costs associated with patients carrying a penicillin allergy label have been identified including higher cost antibiotics in both inpatient and outpatient settings, increased number of antibiotics used during an inpatient admission, use of intravenous over oral antibiotics, and medical care costs associated with more frequent hospital admissions or increased length of stays [43]. Focusing on the antibiotic choice in follow-up primary care visits after de-labeling children with a reported penicillin allergy, Vyles *et al.* [30²²] found a potential cost savings of \$1368 in just a 100-patient case series. Kiepuska *et al.* [44] assessed direct costs of drug-induced skin reactions using a retrospective design evaluating hospitalizations at Warsaw's Military Institute of Medicine from 2002 to 2012, estimating €717/patient as a result of care for these adverse events. Nonsteroidal anti-inflammatory drugs and β -lactam antibiotics were the most frequent drugs identified for the patients included [44]. Finally, Quan and Li [45] described rapidly rising costs of vasopressors in recent years, which may have a major impact on the economics of drug allergy moving forward. Any

researchers using retrospective study designs to describe costs that include epinephrine, ephedrine sulfate, or vasopressin should consider how actual prices reported in the time period compares to current prices as a generic 3% inflation adjustment (commonly used in health economic evaluations) may greatly underestimate the true price inflation for certain products.

Which outcomes?

For cost-effectiveness, combining morbidity and mortality in a single outcome using a measure such as the QALY has been recommended for over 20 years [40,41]. To capture morbidity, quality-of-life measures may be captured through a variety of instruments from broad disease-agnostic tools (EQ-5D, SF-6D, SF-36, HUI) to more disease specific health-related quality-of-life instruments [46]. Recently, Del Pozzo-Magaña *et al.* [47] tested a disease-specific questionnaire for ADR in 112 patients. Chongpison *et al.* [48²²] also evaluated a disease specific quality-of-life tool called the Drug Hypersensitivity Quality of Life (DrHy-Q) Questionnaire in 306 Thai patients diagnosed with drug hypersensitivity. Although an ADR-specific quality-of-life instrument may provide more useful feedback for a clinician, these tools do not reflect a true health utility measure that can be used to estimate a QALY. This may require additional research to validate the tool against traditional utility instruments used in economic evaluations. Beyond health utility, other outcomes may be useful for economic evaluations (reduced hospital length of stay, fewer readmissions, fewer allergic events, and so on) that may need to be considered.

OTHER CONSIDERATIONS

Other aspects of drug allergy economics were identified in this review that may warrant additional discussion or research.

Drug approval and postmarketing safety

Ikedo *et al.* [49] evaluated first-in-class drug approvals by the Food and Drug Administration (FDA) for postmarketing safety issues including all-ADR, drug allergy related ADR, drug-specific ADR, and class-effect ADR. Although drug allergy ADRs observed were not significantly different in first-in-class drugs compared to other drugs approved, this may have been because of the way these events were defined. Postmarketing surveillance of drug allergy may be an area where future research is needed.

Litigation and professional liability

Even despite the substantial efforts in research and changes in practice guidelines, clinicians may still avoid using a β -lactam antibiotic in a patient with a self-reported penicillin allergy. In a recent review of medical negligence and malpractice cases found that practitioners were not found liable when prescribing a cephalosporin or carbapenem in patient with a known penicillin allergy, however three in seven (43%) of the cases where a penicillin-based antibiotic was prescribed the defendants were held liable [50^{***}]. Despite the evidence that few patients have a true hypersensitivity to penicillin, providers may still favor conservative practices (additional testing, and so on) to avoid potential litigation, potentially increasing total health system costs.

Impact on the military

The implications of drug allergy research may be amplified for military operations. Lee *et al.* [51^{***}] recently reviewed the potential for penicillin allergy de-labeling to improve U.S. military readiness. Military operations provide a unique area for drug allergy research as soldiers encounter health services systematically in basic training, planning for combat, during combat, and after active-duty. β -Lactam antibiotics are frequently recommended as first-line therapy for a wide range of common infections a soldier may encounter and medical supplies stocked and ready for use in remote settings are often limited [51^{***}]. The U.S. military includes drug allergies with the medical warnings engraved on soldiers' 'dog tags' and improving the accuracy of these labels may impact health outcomes and overall costs for operations [51^{***}].

CONCLUSION

Studies over the past year provide new opportunities for the field of drug allergy research. The focus of current research to capture direct health costs or savings associated with drug allergy interventions demonstrates opportunity for more cost-effective care delivery and opportunity to explore greater benefits to society. Early interventions and implementation in high cost areas provide 'low hanging fruit' for economic evaluation, but with advances in technology, training across provider types, and evidence-based guidelines we may be able to explore more broad applications and delivery of cost-effective drug allergy practices.

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