

REVIEW ARTICLE

Educational case series: Desensitization to antibiotics in children

Josefina R. Cernadas

Department of Allergy and Clinical Immunology, University Hospital of S.João, Porto, Portugal

To cite this article: Cernadas JR. Educational case series: Desensitization to antibiotics in children. *Pediatr Allergy Immunol* 2012.

Keywords

children; drug allergy; desensitization; protocols

Correspondence

Josefina R. Cernadas, Department of Allergy and Clinical Immunology, H.S.João, Alameda Hernani Monteiro, 4200 Porto, Portugal.
Tel.: +351967050076
Fax: +351222018892
E-mail: josefinacernadas@gmail.com

Accepted for publication 15 July 2012

DOI:10.1111/pai.12001

Abstract

Drug hypersensitivity reactions can occur to almost all drugs and antibiotics are among the most common cause for this kind of reactions. Drug hypersensitivity may affect any organ or system, and manifestations range widely in clinical severity from mild pruritus to anaphylaxis. In most cases, the suspected drug is avoided in the future. In case of infection, there is usually a safe antibiotic alternative. Nonetheless, in some cases, no alternative treatment exists for optimal therapy. Under these circumstances, desensitization may be performed. Drug desensitization is defined as the induction of a temporary state of tolerance to a drug which can only be maintained by continuous administration of the medication responsible for the hypersensitivity reaction. Desensitization is mainly performed in IgE-mediated reactions. Increasing doses of the implicated drug are administered over a short period of time, until the therapeutic dose is achieved and tolerated. Very few studies confined to children are found in literature. Most of them are case reports. In general, the proposed desensitization schemes are similar to those used in adults differing only in the final dose administered. The purpose of this study is to review desensitization to antibiotics in children presenting and discussing three clinical practical cases of desensitization in this age group.

Antibiotics are among the most commonly prescribed drugs in children and are the most likely to be associated with adverse reactions (1–3). Antimicrobial drugs, particularly beta-lactams (BL), are frequently involved in hypersensitivity reactions (4, 5).

In clinical practice, it is a common problem to decide which antibiotics should be used in patients who have been labeled as allergic to these drugs.

Sometimes, such patients are treated with antibiotics there are less effective, more toxic, have a broader spectrum, more side effects, and are more expensive than the drug of first choice (6).

An adverse reaction to a drug is defined as 'any response which is noxious and unintended and which occurs at doses used in man for prophylaxis, diagnosis, or treatment purposes' (7). A reaction to a drug is considered to be allergic if it involves the immunologic system. Basic mechanisms and clinical presentations of antibiotic allergy can be understood according to Gell–Coombs classification (8, 9). Several mechanisms may be involved in the same reaction; however, in most of the cases, this can not be proved.

Although the majority of reactions are not severe enough to lead to hospital admission (10), clinicians often hesitate to prescribe an antibiotic to patients with suspected drug allergy

because of the potential risk of life-threatening anaphylaxis (11–13).

Prevalence

Data concerning drug allergy prevalence is scarce, and the true prevalence of antibiotic allergy is unknown. In ambulatory children followed in prospective studies, the incidence of adverse drug reactions ranges from 0.75% to 4.5% (1–4, 14). In adults, autoreported hypersensitivity to penicillin and other BL was 4.5% (15).

Commonly, the pathophysiologic basis of an adverse drug reaction is not known. The serum sickness-like illness that occurs in about 0.06% of children receiving cefaclor (9, 16) is likely due to a cytotoxic effect of the drug on cells rather than immune complex deposition (17).

The suspected allergy event may also be related to the infectious agent rather than to the drug itself. The rash that appears when amoxicillin is given to patients with Epstein–Barr virus infection is common in children (18, 19). It is possible that some infections can induce an inflammatory state that increases the activation of T cells and initiates an immunologic reaction in a patient who would otherwise not react to that drug (18–20).

Management of drug hypersensitivity

With regard to the diagnosis of hypersensitivity reactions to drugs, the European Network for Drug Allergy (ENDA), the European Academy of Allergy and Clinical Immunology (EAACI) interest group on drug hypersensitivity devised a questionnaire, which has already proved to be very useful for collecting anamnestic data (21). There are different ENDA guidelines for evaluating immediate or non-immediate reactions to BL (22–24). The diagnosis of immediate and non-immediate reactions is based on clinical history, skin tests, in vitro tests, oral provocations, and diagnostic aspects are very well discussed and described in a previous paper by M. Atanaskovic-Markovic (25).

The general rules of management of drug hypersensitivity reactions to antibiotics in children are the same as in adults (26, 27). The main difficulty of the diagnostic workup concerns the performance of intradermal tests in young children, because of pain and discomfort associated with this technique.

If the diagnostic study does not exclude drug allergy, the recommendation is to avoid the culprit antibiotic, as well as those with cross-reactivity, to prevent drug-induced reactions in future uses. A structurally unrelated antibiotic should be prescribed as a safe alternative in the presence of an infection. The majority of the cases can be managed safely by this approach.

If a patient has weak evidence of an antibiotic allergy and is likely to require that antibiotic in the future, rechallenge may be indicated as a standard tool for diagnosis. Rechallenge can be performed during diagnostic workup, or it can be delayed until the patient requires the antibiotic. It should be performed in a proper hospital setting where anaphylaxis can be treated by experienced doctors, especially if the previous reaction could have been IgE-mediated and this could not be proved otherwise.

Desensitization: indications and contraindications

If a patient has a definite or a very likely diagnosis of drug allergy to a particular drug and needs it, desensitization is the only actual way to reintroduce the culprit drug (28, 29).

Drug desensitization is defined as the induction of a temporary state of tolerance to a compound responsible for a hypersensitivity reaction and this state can only be maintained by continuous administration of the medication. This is particularly important for patients to whom a specific drug is essential for optimal therapy. It is indicated when the drug involved is irreplaceable or if it is more effective than possible alternatives (28, 29).

Desensitization is performed by administering increasing doses of the culprit drug over a short period of time (from several hours to a few days), orally whenever possible, until the cumulative therapeutic dose is achieved and tolerated (28, 29).

Desensitization is specially indicated in IgE-mediated reactions but it also seems to work for sulfonamide and other drug reactions thought to be non-IgE-mediated (30–32). Desensitization is absolutely contraindicated in patients who

have experienced severe, life-threatening immunocytotoxic reactions, vasculitis, or bullous skin diseases (33–35).

General rules for antibiotic desensitization in children

Apart from clinical cases, limited data are available on desensitization protocols in children. The most common published protocols relate to antibiotics such as penicillins and non-penicillin BL in cystic fibrosis.

The general rules for rapid drug desensitization discussed in the study of Cernadas et al. (29) also apply to children:

- Before performing any desensitization procedure, be sure that the drug is irreplaceable and is more effective than the alternatives.
- Always make sure that desensitization is associated with the risk of acute hypersensitivity reaction during the procedure.
- Individual risk/benefit evaluation has to be performed, and the benefits must outweigh the risks.
- Caution and surveillance by well-trained specialists is mandatory in all cases, with continuous monitoring of the child.
- Nurses should be trained to recognize early symptoms of hypersensitivity reaction; fathers or tutors accompanying children should be taught to recognize early signs and to notify the nurse or doctor.
- Desensitization for more severe reactions, like anaphylaxis, should be carried out in the intensive care unit (ICU)
- Whenever feasible, desensitization procedures should take into account available protocols, but many times and for specific reasons, protocols may have to be tailor made for each case.
- Before any procedure of this kind, an informed and signed consent, by parents or tutors, is mandatory.

Mechanisms and molecular targets

Despite its clinical success, little is known about the mechanisms and molecular targets of drug desensitization. Mast cells and basophils seem to be targets in the process, because mediators from these cells are released during hypersensitivity reactions as well as during desensitization procedures. Among several described and studied mechanisms, desensitization is thought to be effective, either because IgE is neutralized by the increasing dose of antigen or because mast cells are slowly degranulated, thus provoking milder reactions (36–38).

Practical clinical cases

Case 1

A 5-yr-old boy with a congenital cardiac abnormality, mitral valve prolapse (MVP), seriously ill, was admitted to the hospital and the diagnosis of bacterial endocarditis to *Streptococcus viridans*, highly sensitive to penicillin (Minimum Inhibitory Concentration < 0.1 mg/ml), was made. MIC is the lowest concentration of antimicrobial agent which inhibits the growth of the microorganism.

When MIC to penicillin is between 0.1 and 0.5 mg/ml, these patients are preferentially treated with penicillin for 4 wk and gentamicin in the first 2 wk. Antibiotic therapy was started with crystalline penicillin (200.000 UI/kg/day) in association with gentamicin (4 mg/kg/day).

Fifteen minutes after beginning penicillin infusion, he developed facial flushing, swelling of the lips and urticaria on the trunk and arms, rapidly progressing to the whole body, without other symptoms. He had a previous non-registered history of urticarial rash, 1 yr before, after taking amoxicillin/clavulanic acid, interpreted as a rash associated with a viral infection.

Owing to the severity of the disease, this patient could not be submitted to the usual diagnostic workup of penicillin allergy; blood sample for specific IgE determination to penicilloyl G, penicilloyl V, amoxicilloyl, ampicilloyl, and cefaclor (UniCAP) was collected, and serum tryptase was measured at the time of reaction and 4 days later. The reaction was treated with anti-histamine and corticosteroids, and the infusion was stopped. Because this drug was the treatment of choice for this case, a desensitization protocol by endovenous (IV) route was prepared to begin the next day.

Desensitization with penicillins

The typical symptoms for IgE-induced hypersensitivity reactions to penicillins are pruritus, urticaria, angioedema, and bronchospasm, culminating in various degrees of anaphylaxis. These are the reactions typically eligible for desensitization (28, 29).

Although several specific protocols for desensitization have been widely published for penicillin, the one described by Sullivan (39) is the most well known and used. The oral route seems to be safer, because it is less prone to expose patients to multivalent penicillin conjugates, thought to have an important role in IgE-mediated reactions (40). It is also the preferable route in children, when possible and indicated (Table 1). Classical protocol for oral and intravenous desensitization to penicillin (Tables 1 and 2) start with 1/10.000 to 1/1000 of the target dose, increasing doses by doubling it. Doses are administered every 15–20 min, over the course of several hours, until the therapeutic dose is reached.

Intravenous protocols and protocols with mixed routes are also available (41, 42). Based on the clinical experience with these protocols in adults, they can be adapted for children, considering the adequate dose per kg/day and the clinical status of the patient.

In patients with severe anaphylaxis (such as hypotension with loss of consciousness or severe bronchospasm), the initial dose should begin from 1/1.000.000 to 1/10.000 of the full therapeutic dose (29). When the antibiotic is administered several times per day, desensitization needs to be performed only one time per treatment course. If the desensitization is well succeeded, subsequent doses are administered as prescribed (e.g., 4/4 h).

For the described case, a protocol for IV penicillin (3.600.000 U/day) was prepared and used with success. Penicillin treatment was continued for 4 wk without further

Table 1 Oral penicillin desensitization protocol

Step	Penicillin (mg/ml)	Amount (ml)	Dose (mg)	Cumt dose (mg)
1	0.5	0.1	0.05	0.05
2	0.5	0.2	0.1	0.15
3	0.5	0.4	0.2	0.35
4	0.5	0.8	0.4	0.75
5	0.5	1.6	0.8	1.55
6	0.5	3.2	1.6	3.15
7	0.5	6.4	3.2	6.35
8	5.0	1.2	6.0	12.35
9	5.0	2.4	12.0	24.35
10	5.0	5.0	25.0	49.35
11	50.0	1.0	50.0	100.0
12	50.0	2.0	100.0	200.0
13	50.0	4.0	200.0	400.0
14	50.0	8.0	400.0	800.0

Observe patient for 30 min, then give full therapeutic dose by the desired route. The time interval between doses is 15–20 min (39).

Table 2 Penicillin intravenous desensitization protocol using a continuous infusion pump

Step	Penicillin (mg/ml)	Flow rate (ml/h)	Dose (mg)	Cumulative dose (mg)
1	0.01	6	0.015	0.015
2	0.01	12	0.03	0.045
3	0.01	24	0.06	0.105
4	0.1	50	0.125	0.23
5	0.1	10	0.25	0.48
6	0.1	20	0.5	1.0
7	0.1	40	1.0	2.0
8	0.1	80	2.0	4.0
9	0.1	160	4.0	8.0
10	10.0	3	7.5	15.0
11	10.0	6	15.0	30.0
12	10.0	12	30.0	60.0
13	10.0	25	62.5	123.0
14	10.0	50	125.0	250.0
15	10.0	100	250.0	500.0
16	10.0	200	500.0	1000.0

Observe patients, then give full therapeutic dose by the desired route. Interval between doses is 15–20 min (41).

reactions. Mild reactions have been reported in 30–80% of penicillin-allergic patients undergoing desensitization, but most of the desensitization procedures were completed with success (43, 44).

In this patient, tryptase level after the reaction was 14 µg/l (<11.4 µg/l) and specific IgE for penicilloyl G was 3.5 kU/l (<0.35 kU/l). As stated before, the definitive diagnosis of an IgE-mediated reaction could only have been performed several weeks later when the child was stable. It would be necessary to perform cutaneous tests to benzilpenicillin, major and minor determinants, and also to amoxicillin, along with in

Table 3 Twelve-step protocol for ceftazidimeName of medication: *Ceftazidime*

					Total mg per bag	Amount of bag infused (ml)
Solution 1: 100 ml of 0.200 mg/ml					20.00	9.25
Solution 2: 100 ml of 2.000 mg/ml					200.00	18.75
Solution 3: 100 ml of 19.607 mg/ml					1960.65	250.00
Step	Solution	Rate (ml/h)	Time (min)	Volume infused per step (ml)	Dose administered with this step (mg)	Cumulative dose (mg)
1	1	2.0	15	0.50	0.100	0.100
2	1	5.0	15	1.25	0.250	0.350
3	1	10.0	15	2.50	0.500	0.850
4	1	20.0	15	5.00	1.000	1.850
5	2	5.0	15	1.25	2.500	4.350
6	2	10.0	15	2.50	5.000	9.350
7	2	20.0	15	5.00	10.000	19.350
8	2	40.0	15	10.00	20.000	39.350
9	3	10.0	15	2.50	49.016	88.366
10	3	20.0	15	5.00	98.0325	186.399
11	3	40.0	15	10.00	196.065	382.464
12	3	80.0	61.87	82.50	1617.536	2000.00
Total time = 226.875 min (3 h 46 m)						

A safe protocol for rapid desensitization in patients with cystic fibrosis and antibiotic hypersensitivity by Legere et al. (45).

vitro tests assays for specific IgE for penicilloyl G, penicilloyl V, amoxicilloyl, with UniCAP (Phadia, Uppsala, Sweden).

In this particular case, the final diagnosis of IgE-mediated reaction to BL antibiotic was confirmed when the patient was inadvertently medicated with amoxicillin/clavulanic acid for tonsillitis, with appearance of generalized urticaria less than 30 minutes after first intake.

Case 2

A 12-yr-old boy, followed in the Allergy Department with the diagnosis of atopic rhinoconjunctivitis (allergic to house dust mites) and asthma, since the previous year. His clinical and functional state progressively worsened (FEV1 of 53%) and the diagnosis of cystic fibrosis (CF) was made and confirmed by genetic study. Bacterial exams of sputum showed *Pseudomonas aeruginosa* (Pa) and double scheme of antibiotics consisting of tobramycin (3 mg/kg q8h) associated with meropenem (40 mg/kg q8h) was prescribed. His clinical state stayed unchanged, and cultures of sputum were still positive to Pa, now resistant to meropenem. Pulmonologist decided to change to ceftazidime 50 mg/kg q8h plus tobramycin. At the first and second exacerbation of CF, this therapeutic scheme improved clinical, functional and radiologic signs.

At the third exacerbation, soon after antibiotic infusion with ceftazidime he developed cutaneous (flushing, pruritus, urticaria, and angioedema) and respiratory (sneezing, nasal congestion, dyspnea, coughing, wheezing, and oxygen desaturation) symptoms.

Patient was eligible to rapid desensitization based on a clinical history consistent with a type I hypersensitivity reaction, although skin tests were not feasible, nor indicated at the time. The same antibiotic was chosen by the consulting pulmonologist based on sensitivity pattern of the bacterial pathogen. The desensitization procedure was performed according to Legere's et al. (45) twelve-step protocol (Table 3), using pediatric dosage of ceftazidime – 50 mg/kg q8h, and full antibiotic dose was administered and continued with tolerance.

Desensitization with non-penicillins betalactams

Although hypersensitivity reactions to non-penicillin BL antibiotics have been reported less frequently, there are some cases in the literature of successful desensitization to non-penicillin BL antibiotics such as meropenem, cefotaxime, ceftriaxone, and ceftazidime (46–48). Most of these reactions were IgE-mediated.

Children and young adolescents with CF have a higher prevalence, up to 70%, of allergic reactions to one or multiple antibiotics, especially BL, thought to be due in part to multiple and repeated exposures (49, 50).

The high incidence of pseudomonal infections, the consequent need to treat with specific antipseudomonal antibiotics, and the risk of potentially life-threatening allergic reactions often complicate the treatment of these patients with a frequently need for desensitization procedures.

Moreover, because most of these patients have significantly impaired lung function and increased risk of anaphylaxis,

desensitization must be carefully conducted to induce tolerance to first-line therapy. The choice of antibiotic is determined by the consulting pulmonologist, based on the antibiotic sensitivity of the bacterial pathogen.

The indication for desensitization is almost exclusively guided by the clinical history, as skin tests are not indicated at the time of the reaction.

There is already some data on desensitization experience with non-penicillin BL antibiotics in patients with CF; protocols are different in terms of initial doses, dose increments, number of steps (6–12 steps), use of premedications, and success rate that ranges from 75% to 100% (45, 51, 52).

Desensitization procedure will be needed each time ceftazidime use is required.

Case 3

A 3-yr-old girl was admitted at the infectiology department for suspected tuberculous meningitis. She had presented with fever, vomiting, poor appetite, irritability, abdominal pain, and headaches for several days. Her clinical status, rapidly deteriorated and she was admitted to the ICU in coma. Tuberculous meningitis was assumed, after all diagnostic exams were performed, including lumbar puncture and, even before diagnostic confirmation, as it is a medical emergency, empirical antituberculosis therapy was promptly started. She began a four drug therapy scheme with isoniazid, rifampicin, pyrazinamide, and ethambutol. Doses were adjusted according to age and weight. On the third day of therapy, and consistent with rifampicin administration, she developed an intense, generalized urticarial rash and the Allergist was called. As it was not possible to suspend all four drugs, the most probable one was withdrawn (rifampicin) and skin lesions were treated with antihistamines and corticosteroids with complete resolution of skin reaction in 3 days. Soon after, at the 4th day, rifampicin 200 mg was reintroduced according to a planned tolerance induction scheme, beginning with 2 mg of a rifampicin suspension and doubling dosage until 200 mg/day was reached.

Desensitization with anti-tuberculosis drugs

Tuberculous meningitis (TBM) is a medical emergency. It is a severe disease with possible fatal outcome and prompt treatment is essential, even before definitive diagnosis. A high index of clinical suspicion is absolutely essential because treatment delay is strongly associated with death. Empirical antituberculosis therapy should be started promptly in all patients in whom the diagnosis of TBM is suspected, without waiting for microbiological or molecular diagnostic confirmation. Isoniazid, rifampicin, and pyrazinamide are considered mandatory at the beginning of TBM treatment. For the choice of the fourth drug, most authorities recommend either streptomycin or ethambutol (53).

Isoniazid (10–15 mg/kg to a maximum of 300 mg/day) and rifampicin (10–20 mg/kg to a maximum of 600 mg/day) pyrazinamide (30–40 mg/kg), and ethambutol (15–25 mg/kg) are reported to be well tolerated in children and are the key components of the treatment scheme (53).

As treatment requires administration of multiple drugs simultaneously, hypersensitivity reactions have been reported in up to 5% of the patients. Non-immediate and immediate reactions, mostly urticarial rashes, are seen with these drugs, predominantly with rifampicin (4, 5).

If an adverse drug reaction occurs in a child taking antimicrobial agents, a careful clinical assessment should be performed to determine whether the clinical event is a drug reaction potentially allergic in nature. The diagnosis is mostly based on, after stopping all medications, recurrence of the symptoms when drugs are reintroduced, one at a time, with a 4–5 days interval. The nature of the reaction should be carefully documented in the child's health record.

Our case 3 refers to a young girl, with tuberculous meningitis (TBM), admitted in the ICU, and treated with multiple drugs. Close monitoring in the ICU allowed to establish a possible relationship between cutaneous signs and rifampicin administration. Owing to the severity of the underlying condition, stopping all drugs, with the re introduction, one at a time, with a 4–5 days interval, was not possible.

TBM may have an acute presentation or a more indolent prodrome, usually with non-specific symptoms and signs. There should be a strong suspicion whenever patient presents with a clinical picture of meningoencephalitis, especially in high-risk groups. Confirmation of diagnosis occurs very often after treatment has been instituted. The risk factor in our patient was a very poor social economic background.

After evaluating the risk/benefit and the probability of drug reaction to rifampicin, this drug was stopped, cutaneous signs and symptoms were treated and 4 days later rifampicin was reintroduced according to an adapted tailor made protocol for rifampicin tolerance induction.

Conclusions

Drug desensitization is the induction of a temporary state of tolerance to a compound responsible for a hypersensitivity reaction. There are few published clinical cases of desensitization in children of young age. Most published studies refer to desensitization with antibiotics in adults and even so, standardized protocols are not yet available. A high success rate has been reported in series of patients sensitized to BL, but failures and life-threatening anaphylaxis have also been described. Desensitization is a high-risk procedure and should be used only by well-trained doctors in selected patients when alternatives are less effective or not available, and after establishing a risk/benefit analysis. Only few fatalities have been reported, all of which related to the underlying disease. Despite this, the majority of desensitization protocols with antibiotics were able to induce tolerance and cause minor adverse reactions during the procedure, easily treatable, with no need to stop the desensitization procedure.

The selection of candidates for desensitization by allergists, the control of concomitant diseases, the training of personnel (doctors and nurses), the treatment of breakthrough reactions, and the availability of validated protocols are crucial for the success of this procedure. Both successful and unsuccessful outcomes should be published, to establish the most

efficient and safer protocols. Although literature is scarce concerning desensitization in children, the author suggests that the general rules and protocols applied for adults can be adapted for children, considering children's specificities.

Acknowledgment

The author wish to thank Ana Luisa Reis Ferreira for English revision of this manuscript.

References

- Kramer MS, Hutchinson TA, Flegel KM, Naimark L, Contardi R, Leduc DG. Adverse drug reactions in general pediatric outpatients. *J Pediatr* 1985; **106**: 305–10.
- Cirko-Begovic A, Vrhovac B, Bakran I. Intensive monitoring of adverse drug reactions in infants and preschool children. *Eur J Clin Pharmacol* 1989; **36**: 63–5.
- Menniti-Ippolito G, Raschetti R, Da Cas R, Giaquinto C, Cantarutti L. Active monitoring of adverse drug reactions in children. Italian Paediatric Pharmacosurveillance Multicenter Group. *Lancet* 2000; **355**: 1613–43.
- Gruchalla RS, Pirmohamed M. Clinical practice. Antibiotic allergy. *N Engl J Med* 2006; **354**: 601–9.
- Çelik G, Adkinson F. Hypersensitivity to antibiotics. In: Clinical Infectious Disease in eds: David Schlossberg 2008: 1445–56.
- Preston SL, Briceland LL, Lesar TS. Accuracy of penicillin allergy reporting. *Am J Hosp Pharm* 1994; **51**: 79–84.
- Karch FE, Lasagna L. Adverse drug reactions. A critical review. *JAMA* 1975; **234**: 1236–41.
- Shepherd GM. Allergy to b-lactam antibiotics. *Immunol Allergy Clin North Am* 1991; **11**: 611–33.
- Kearns GL, Wheeler JG, Childress SH, et al. Serum sickness-like reactions to cefaclor: role of hepatic metabolism and individual susceptibility. *J Pediatr* 1994; **125**: 805–11.
- Mitchell AA, Lacouture PG, Sheehan JE, Kauffman RE, Shapiro S. Adverse drug reactions in children leading to hospital admission. *Pediatrics* 1988; **82**: 24–9.
- Solensky R, Earl HS, Gruchalla RS. Clinical approach to penicillin allergic patients: a survey. *Ann Allergy Asthma Immunol* 2000; **84**: 329–33.
- Wickern GM, Nish WA, Bitner AS, Freeman TM. Allergy to beta-lactams: a survey of current practices. *J Allergy Clin Immunol* 1994; **94**: 725–31.
- Kraemer M, Caprye-Boos H, Berman H. Increased use of medical services and antibiotics by children who claim a prior penicillin sensitivity. *West J Med* 1987; **146**: 697–700.
- Woods CG, Rylance ME, Cullen RE, Rylance GW. Adverse reactions to drugs in children. *BMJ* 1987; **294**: 869–70.
- Gomes E, Cardoso MF, Praça F, Gomes L, Mariño E, Demoly P. Self-reported drug allergy in a general adult Portuguese population. *Clin Exp Allergy* 2004; **34**: 1597–1601.
- Prober C. Cephalosporins: an update. *Pediatr Rev* 1998; **19**: 118–27.
- Borish L. Immune mechanisms of drug allergy. *Immunol Allergy Clin North Am* 1998; **18**: 717–29.
- Jappe U. Amoxicillin-induced exanthema in patients with infectious mononucleosis: allergy or transient immunostimulation? *Allergy* 2007; **62**: 1474–5.
- Shiohara T, Takahashi R, Kano Y. Drug hypersensitivity. In: Pichler W, ed. Drug Induced Hypersensitivity Syndromes and Viral Reactivation. Bern: Karger Verlag, 2007: 251–66.
- González-Delgado P, Blanes M, Soriano V, Montoro D, Loeda C, Niveiro E. Erythema multiforme to amoxicillin with concurrent infection by Epstein-Barr virus. *Allergol Immunopathol (Madr)* 2006; **34**: 76–8.
- Demoly P, Krope R, Bircher A, Pichler WJ. Drug hypersensitivity questionnaire. *Allergy* 1999; **54**: 999–103.
- Torres MJ, Blanca M, Fernandez J, et al. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. Position paper. *Allergy* 2003; **58**: 961–72.
- Blanca M, Romano A, Torres MJ, et al. Update on the evaluation of hypersensitivity reactions to betalactams. *Allergy* 2009; **64**: 183–93.
- Romano A, Blanca M, Torres MJ, et al. Diagnosis of nonimmediate reactions to beta-lactam antibiotics. *Allergy* 2004; **59**: 1153–60.
- Atanaskovic-Markovic M. Educational case series: b-lactam allergy and cross-reactivity. *Pediatr Allergy Immunol* 2011; **22**: 770–5.
- Çelik G, Pichler WJ, Adkinson NF Jr. Drug Allergy. In: Adkinson NF Jr, Busse W, Bochner S, Holgate S, Lemanske R, Simons E eds. Middleton's Allergy: Principles and Practice 7th ed 2008: 1205–23.
- Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol* 2010; **105**: 259–73.
- Castells M. Rapid desensitization for hypersensitivity reactions to medications. *Immunol Allergy Clin North Am* 2009; **29**: 585–06.
- Cernadas JR, Brockow K, Romano A, et al. General considerations on rapid desensitization for drug hypersensitivity – a consensus statement. *Allergy* 2010; **65**: 1357–66.
- Demoly P, Messaad D, Sahla H, et al. Six-hour trimethoprim- sulfamethoxazole graded challenge in HIV-infected patients. *J Allergy Clin Immunol* 1998; **102**: 1033–6.
- Berges-Gimeno MP, Stevenson DD. Nonsteroidal anti-inflammatory drug induced reactions and desensitization. *J Asthma* 2004; **41**: 375–84.
- Berges-Gimeno MP, Simon RA, Stevenson DD. Long-term treatment with aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2003; **111**: 180–6.
- Solensky R. Drug hypersensitivity. *Med Clin North Am* 2006; **90**: 233–60.
- Adkinson NF Jr. Allergy, principles and practice. In: Middleton E Jr, Adkinson NF Jr, Yunginger JW, Busse WW, Bochner BS, Holgate ST, Simons ER, eds. Drug Allergy. New York: Mosby Co, 2003: 1679–94.
- Pichler WJ, Yawalkar N, Britschgi M, et al. Cellular and molecular pathophysiology of cutaneous drug reactions. *Am J Clin Dermatol* 2002; **3**: 229–38.
- Patterson R, DeSwarte R, Greenberger P, Grammer L, Brown J, Choy AC, eds. Drug Allergy and Protocols for Management of Drug Allergies, 2nd edn. Providence, RI: Oceanside, 1995.
- Sobotka A, Dembo M, Goldstein B, Lichtenstein L. Antigen specific desensitization of human basophils. *J Immunol* 1979; **122**: 511–7.
- Shalit M, Levi-Schaffer F. Challenge of mast cells with increasing amounts of antigen induces desensitization. *Clin Exp Allergy* 1995; **25**: 896–02.
- Sullivan TJ, Yecies LD, Shatz GS, Parker CW, Wedner HJ. Desensitization of patients allergic to penicillin using orally administered beta-lactam antibiotics. *J Allergy Clin Immunol* 1982; **69**: 275–82.
- Sullivan TJ. Allergy, principles and practice. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, eds. Drug Allergy. St. Louis: Mosby Co, 1993: 1726–46.
- Solensky R. Drug desensitization. *Immunol Allergy Clin North Am* 2004; **24**: 425–43.
- Solensky R. Drug hypersensitivity. In: Pichler W, ed. Desensitization with Antibiotics. Bern: Karger Verlag, 2007: 404–12.
- Naclerio R, Mizrahi EA, Adkinson NF Jr. Immunologic observations during desensitization and maintenance of clinical tolerance

- to penicillin. *J Allergy Clin Immunol* 1983; **71**: 294–01.
44. Stark BJ, Earl HS, Gross GN, Lumry WR, Goodman EL, Sullivan TJ. Acute and chronic desensitization of penicillin-allergic patients using oral penicillin. *J Allergy Clin Immunol* 1987; **79**: 523–32.
 45. Legere HJ, Palis RI, Rodriguez Bouza T, Uluer AZ, Castells MC. A safe protocol for rapid desensitization in patients with cystic fibrosis and antibiotic hypersensitivity. *J Cyst Fibros* 2009; **8**: 418–24.
 46. Wilson DL, Owens RC Jr, Zuckerman JB. Successful meropenem desensitization in a patient with cystic fibrosis. *Ann Pharmacother* 2003; **37**: 1424–8.
 47. Ghosal S, Taylor CJ. Intravenous desensitization to ceftazidime in cystic fibrosis patients. *J Antimicrob Chemother* 1997; **39**: 556–7.
 48. Rodrigues JC, Cruz LG, Botelho C, Rio E, Castel-Branco MG. Successful desensitization to ceftriaxone in a patient with doxycycline resistant Lyme disease. *Allergol Immunopathol* 2009; **37**: 105–6.
 49. Parmar JS, Nasser S. Antibiotic allergy in cystic fibrosis. *Thorax* 2005; **60**: 517–20.
 50. Burrows JA, Nissen LM, Kirkpatrick CM, Bell SC. Beta-lactam allergy in adults with cystic fibrosis. *J Cyst Fibros* 2007; **6**: 297–3.
 51. Whitaker P, Shaw N, Gooi J, Etherington C, Conway S, Peckham D. Rapid desensitization for non-immediate reactions in patients with cystic fibrosis. *J Cyst Fibros* 2011; **10**: 282–5.
 52. Burrows JA, Toon M, Bell SC. Antibiotic desensitization in adults with cystic fibrosis. *Respirology* 2003; **8**: 359–64.
 53. Thwaites G, Fisher M, Hemingway C, et al. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. *J Infect* 2009; **59**: 167–87.