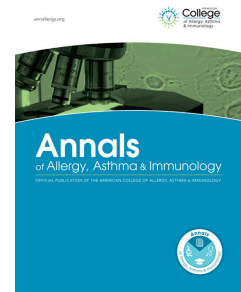


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Title: A revision of rapid colistin desensitization

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Polymyxins, namely colistimethate sodium (colistin or polymyxin E) and polymyxin B, are used for multi-drug resistant gram-negative bacterial infections, including *Pseudomonas aeruginosa* and *Acinetobacter baumannii*¹. As treatments and therapy have advanced, patients with cystic fibrosis are living longer. However, these patients have high exposure to intravenous antibiotics, most commonly penicillins, cephalosporins, and aminoglycosides. With colonization or infections with resistant gram-negative bacilli, the exposure to antibiotics broadens to include the polymyxins. Unfortunately, repeated exposures to these antibiotics have been found to be associated with an increased number of hypersensitivity reactions to polymyxins².

Since their discovery in 1947, polymyxins have been found to have both nephrotoxic and neurotoxic effects with minimal potential for hypersensitivity reactions. A study published in 1970 noted an adverse event rate of 2.2% with 25.1% of those being allergic reactions³. Another study described 5-10% of patients treated with colistin having an allergic reaction, with 40% of those being dermal reactions². Subsequent case reports have included reactions of pruritus (in up to 22% of patients receiving IV colistin), rash, contact dermatitis, pneumonitis, cough, bronchoconstriction, and angioedema^{1-2,4-6}. In addition, hypersensitivity reactions to polymyxins are more common in those with known bacitracin allergy due to cross-reactivity between bacitracin and colistin¹.

Typically, withdrawal of polymyxin and supportive therapy are adequate treatment for adverse events. However, in patients with cystic fibrosis who require double anti-pseudomonal coverage, polymyxins (in particular, colistin) are required¹ and colistin desensitization for induction of temporary drug tolerance is warranted. The first reported drug desensitization was published in 1946 using penicillin⁷. As new anti-microbials are released and used more frequently in patient care, the protocol for desensitization continues to expand. Herein, we report

a case of hypersensitivity reaction to colistin with successful rapid desensitization and completion of planned therapy. We highlight an error of concentration in a previous protocol for rapid intravenous (IV) desensitization to colistin⁸, as it is an important tool for a clinician to have a successful set protocol.

A 55-year-old male with cystic fibrosis, chronic obstructive pulmonary disease, asthma, hearing loss, and depression presented to our tertiary care hospital with increasing productive cough, hemoptysis and dyspnea and was admitted for a cystic fibrosis exacerbation. He was started on IV meropenem 2 grams(g) every 8 hours for *Serratia marcescens* along with IV colistin 45mg every 8 hours as double coverage for *Pseudomonas aeruginosa* that were both found in sputum culture. The patient had previously tolerated both antibiotics with possible drug reaction history of chest tightness from inhaled colistin. The patient experienced perioral itching with each administration of colistin and received scheduled oral diphenhydramine 25 mg every 8 hours. On day 11 of therapy while on oral antihistamine, the patient developed a pruritic rash of the arms, trunk, waist, and thighs within 2 hours of receiving IV colistin and 3 hours of receiving IV meropenem. The rash was erythematous, blanching, well-circumscribed and maculopapular. The patient did not have any respiratory, gastrointestinal, or cardiovascular distress and vital signs were stable. Both antibiotics were stopped and the patient treated with IV methylprednisone and IV diphenhydramine with improvement of rash within 2 hours. Given a prior clinical reaction of perioral itching with administration of colistin and the onset of timing of the rash, colistin was suspected to be the culprit drug. To test for immediate hypersensitivity, skin testing to colistin was performed first, followed by drug challenge for confirmation of the diagnosis.

Both skin prick testing (SPT) with 75mg/mL of colistin and intradermal testing (ID) with 0.25mg/mL of colistin, while the patient had a negative response to the negative control (saline) and a positive response to the positive control (histamine). However, SPT using colistin has not been validated, and he was given anti-histamines in days prior to testing, limiting the validity of SPT. The patient underwent an unblinded drug challenge to IV colistin, with 0.45mg as the initial dose (1/100th of the target dose) and 45mg as the second/final dose after 30 minutes between doses. He developed urticaria on his right wrist and low back 45 minutes after administration of the 2nd dose. This reaction was consistent with a possible Type-I IgE-mediated, though unproven, hypersensitivity reaction and deemed a failure of the drug challenge. Desensitization to colistin was warranted for this cystic fibrosis patient for double anti-pseudomonal coverage and inability to take alternative agents due to severe adverse side effects.

The patient was admitted to the medical intensive care unit (MICU) and underwent an IV colistin desensitization adapted from the previously published protocol by *Tosi et al*⁷. Initial infusion rate of IV colistin was set for 10 mL/hr over 15 minutes at a concentration of 0.00006mg/mL for a total of 0.00015mg of colistin as the first dose (Table 1). The dose was doubled every 15 minutes for a total of 28 doses, with 80 mg as the cumulative dose. The patient passed the desensitization without any reactions and without the use of any antihistamines, steroids, or epinephrine. Intravenous colistin was resumed at 45 mg every 8 hours. He completed the 2-week course successfully without further reactions.

He had an exacerbation of cystic fibrosis requiring use of IV colistin for effective treatment due to inhaled colistin leading to chest tightness. He was not a candidate for tobramycin with history of auditory disturbances. He passed the skin testing (SPT/ID) and failed the drug challenge to colistin. Through the latter, our patient was confirmed to have a type I-

immediate hypersensitivity reaction to colistin and the patient subsequently underwent desensitization. The previously published protocol by *Tosi et al*⁸ was reviewed and an error in the concentration was noted. Doses 1-5 in column 2 of the Tosi protocol under “Colistin concentration infused (mg/mL)” showed 0.0006mg/mL⁸ as the concentration infused instead of 0.00006mg/mL. The appropriate corrections were calculated and an adapted protocol was made for this desensitization (Table 1).

This case reports a calculation error and provides an updated corrected version of the protocol. We further support the use of colistin desensitization in individuals with an immediate hypersensitivity response to colistin who require colistin for anti-microbial therapy.

References

- [1] Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. *Critical Care*. 2006; 10: R27.
- [2] Roehmel JF, Schwarz C, Mehl A, Stock P, Staab D. Hypersensitivity to antibiotics in patients with cystic fibrosis. *J Cyst Fibros*. 2014; 13: 205-211.
- [3] Koch-Weser J, Sidel VW, Federman EB, Kanarek P, Finer DC, Eaton AE. Adverse effects of sodium colistimethate. *Ann Intern Med*. 1970; 72: 857-868.
- [4] Sowa J, Tsuruta D, Kobayashi H, Ishii M. Allergic contact dermatitis caused by colistin sulfate and bacitracin. *Contact Dermatitis*. 2005; 53: 175-176.
- [5] Leong KW, Ong S, Chee HL, Lee W, Kwa AL. Hypersensitivity pneumonitis due to high dose colistin aerosol therapy. *Int J Infect Dis*. 2010; 14: 1018-1019.
- [6] Justo JA, Bosso JA. Adverse reactions associated with systemic polymyxin therapy. *Pharmacotherapy*. 2015; 35: 28-33.
- [7] O'Donovan WJ, Klorfajn I. Sensitivity to penicillin: anaphylaxis and desensitization. *Lancet* 1946; 444-6.
- [8] Tosi MF, Konstan MW, Paschall VL. Rapid intravenous desensitization to colistin. *Ann Allergy Asthma Immunol*. 2012; 109: 359-363.

Dose Number	Colistin Concentration (mg/mL)	Infusion rate (mL/hour)	Infusion duration (hour)	Volume (mL)	Colistin given this interval (mg)	Cumulative colistin given (mg)
1	0.00006*	10	0.25	2	0.00015	0.00015
2	0.00006*	20	0.25	5	0.0003	0.00045
3	0.00006*	40	0.25	10	0.0006	0.00105
4	0.00006*	80	0.25	20	0.0012	0.00225
5	0.00006*	160	0.25	40	0.0024	0.00465
6	0.002	10	0.25	2	0.005	0.0096
7	0.002	20	0.25	5	0.01	0.0196
8	0.002	40	0.25	10	0.02	0.0396
9	0.002	80	0.25	20	0.04	0.0796
10	0.002	160	0.25	40	0.08	0.1596
11	0.064	10	0.25	2	0.16	0.32
12	0.064	20	0.25	5	0.32	0.64
13	0.064	40	0.25	10	0.64	1.28
14	0.064	80	0.25	20	1.28	2.56
15	0.064	160	0.25	40	2.56	5.12
16	2.0	10	0.25	2	5	10
17	2.0	20	0.25	5	10	20
18	2.0	40	0.25	10	20	40
19	2.0	80	0.25	20	40	80

Table 1. Corrected protocol for rapid intravenous desensitization to IV colistin

*change in concentration listed compared to previous protocol