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# Is there a role of penicillin allergy in developing *Clostridioides difficile* infection?

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**Abstract**
Purpose of review: To explore the evidence for an association between penicillin allergy, antibiotic prescribing and *Clostridioides difficile* (CDI) infection.

Recent findings: Several studies have highlighted the differences in antibiotic prescribing in penicillin allergic patients and the impact on rates of *C. difficile* infection.

Summary: Penicillin allergy leads to higher incidences of prescriptions for antibiotics that are known to predispose to CDI. In turn CDI is more common in patients with penicillin allergy. Penicillin allergy is often erroneously ascribed to patients and should be challenged.

Key words: Penicillin allergy, Clostridioides difficile

## Introduction

*Clostridioides difficile* infection (CDI) remains a major global healthcare burden with 12,275 cases reported across English NHS trusts in 2018-2019 and the US Center for Disease Control and Prevention citing it as an urgent threat to public health with 223,900 cases and 12,800 deaths in 2019[1,2].

A major driver for the development of CDI is antibiotic exposure. *C. difficile* is not considered part of the normal adult gut flora and indeed a healthy microbiota appears protective against the acquisition of *C. difficile*[3]. Patients exposed to *C. difficile* spores, often, though not invariably through health care contact, become vulnerable to CDI due to antibiotic treatment which interferes with the normally protective gut flora[4,5]. Different antibiotic classes confer different risks towards developing CDI. Agents such as clindamycin and fluoroquinolones have been ranked amongst the highest risk antibiotics in both community and hospital settings for causing CDI, with penicillins, especially narrow spectrum varieties, being considered safer alternatives[6–8].

## Antibiotic Prescribing in Patients with CDI

Amoxicillin remains the most commonly prescribed antibiotic in the UK due to its low cost and good safety profile[9]. The prevalence of penicillin allergy among primary care

patients in the UK is 5.9% - amounting to 3 million patients[10]. For this cohort, clinicians usually rely on second line antibiotics, which are frequently more toxic and broad spectrum[11–14]. Clindamycin, cephalosporins, quinolones and carbapenems – all regarded as high risk for CDI – are prescribed at considerably higher rates in penicillin allergic patients compared to their non-allergic counterparts[13–15]. While different studies report different statistical measures, these findings have been described in both community and hospitalised patients and across different countries.

Amongst English community patients, West *et al* report the relative risk of being prescribed quinolones in penicillin allergic patients as 2.10 [95% CI 2.02 – 2.19] higher when compared to their non-allergic cohort[10]. Likewise, Su et al report an odds ratio of 2.59 (95% CI 1.22–5.48) for being prescribed quinolones in penicillin allergic Dutch community patients[10,13].
In the hospital setting in the USA, Shah *et al* found a that the relative risk of being prescribed clindamycin was 3.8 [95% CI 3.6–4.0] times that of non-allergic patients and in a UK hospital setting Powell *et al* described penicillin allergic patients as being at 6 times the odds of being prescribed meropenem compared to their counterparts[11,15].

**CDI in Penicillin Allergic Patients**
Patients with penicillin allergy have been shown to have poorer health outcomes compared to their matched cohort in both community and hospital settings, including a significantly increased 1 year mortality and higher rates of *C. difficile* isolation[12,14]. In a cohort of 64,141 UK general practice patients, Blumenthal *et al* described the multivariable adjusted hazard ratio for acquiring CDI in penicillin allergic patients versus their matched cohort as 1.26 (95% confidence interval 1.12 – 1.40)[14]. A large retrospective matched cohort study of over 100,000 UK community patients by West *et al* also found a higher rate of CDI in penicillin allergic patients, but this was not statistically significant, possibly due to the one-year follow up period compared to Blumenthal's longitudinal study design[10]. In a multi-centre hospital cohort study in the US, Macy et al found a 23.4% (95% CI 15.6 to 31.7) increase in the prevalence of CDI compared to a matched non-penicillin allergic cohort[12,14].

It is likely that penicillin allergy increases the risk of acquisition of CDI by increasing the exposure to antibiotics such as carbapenems, quinolones and clindamycin, which harm the healthy gut microbiome and give a competitive advantage to *C. difficile*. Much of the increased usage of antibiotics that are high risk for CDI in patients who are labelled penicillin allergic is likely to be unnecessary, as the majority of such patients do not have a true penicillin allergy: Meta-analysis of 24 studies has shown that the vast majority of penicillin allergic patients do not have a true allergy and completed a negative penicillin skin prick test[16]. A significant number of patients are thus unnecessarily receiving antibiotics that are harmful by promoting CDI, but also MRSA, VRE and multi drug resistant enterobacterales.

Given the prevalent nature of erroneous penicillin allergy labels and its negative health implications, it is imperative that clinicians interrogate every penicillin allergy by taking a thorough history and if uncertainty remains, by referring for timely testing. Penicillin

allergy testing can safely remove a dubious penicillin allergy label and is reliable, but it remains underutilised, in part due to clinicians' lack of knowledge of the test and referral criteria, due to the availability of alternative antibiotics and likely due to an under appreciation of the side effect profile of different antibiotic classes[17]. Potential adverse reactions to penicillins need to be documented clearly and investigated further if appropriate[18]. Correcting spurious penicillin allergy records could be a simple step towards reducing *C. difficile* infection.

**Conclusion**

Penicillin allergic patients are prescribed more antibiotics that predispose to CDI compared to their non-allergic counterparts. This in turns results in higher rates of CDI in penicillin allergic patients. Most cases of documented penicillin allergy are inaccurate and correcting these by referring for appropriate testing may be a way towards reducing rates of CDI.

**Key Points**

1. *C. difficile* infection still presents a significant healthcare burden
2. Being labelled as "penicillin allergic" leads to more frequent prescriptions of antibiotics that are a higher risk for CDI.
3. Penicillin allergy is associated with higher rates of CDI.
4. In the vast majority of cases, patients are incorrectly labelled as penicillin allergic and the allergy status should be challenged by allergy testing.

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