Most patients tolerate penicillin administration despite history of non-anaphylactic penicillin allergy: a systematic review and meta-analysis

Martha DesBiens MD[1,2], Okechukwu Erinne MD[2], Andrew Glick BS[2], Saiganesh Ravikumar BA, BS[2], Peter Scalia MSc.[2]
[1]Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA; [2]The Dartmouth Institute for Health Policy and Clinical Practice, Lebanon, NH, USA

Background

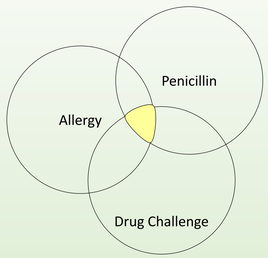
- True allergy to penicillin is rare, despite the high frequency with which it is reported.
- While around 10% of the US population report an allergy to penicillin, only 1% have a true type 1 hypersensitivity to this antibiotic class.
- Misrepresented allergy drives unnecessary use of alternative antibiotics, with profound impacts on clinical outcomes and antibiotic stewardship.
- Tolerance of penicillin administration in patients reporting allergy history, but at low risk for serious drug reactions is not well understood.
- We aim to estimate frequency of full tolerance of systemic drug challenge in patients with reported allergy to penicillin, with low risk of type 1 hypersensitivity or other serious drug reactions.

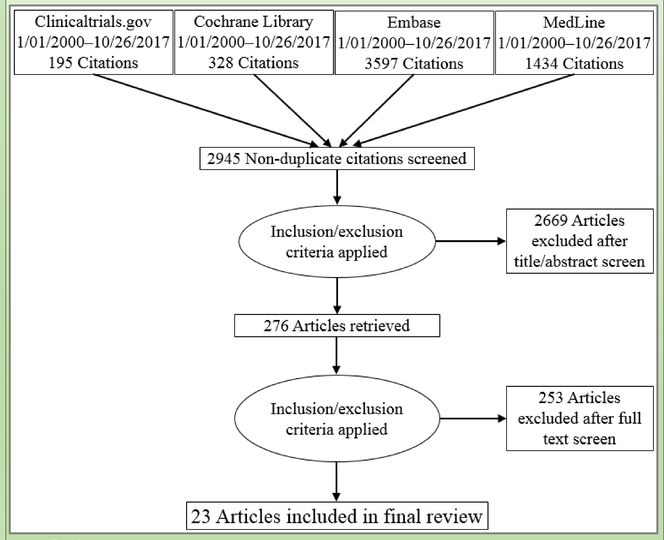
Methods

Study Eligibility and Data Collection:

- Clinical trials, observational studies, cross-sectional studies, quasi-experimental were considered
- Studies were included if they:
  - Evaluated participants with history of penicillin allergy
  - Reported outcomes of tolerance after systemic drug challenge
- Data were extracted by at least two independent reviewers
- Risk of bias was assessed with ECRI tool

Search Strategy:





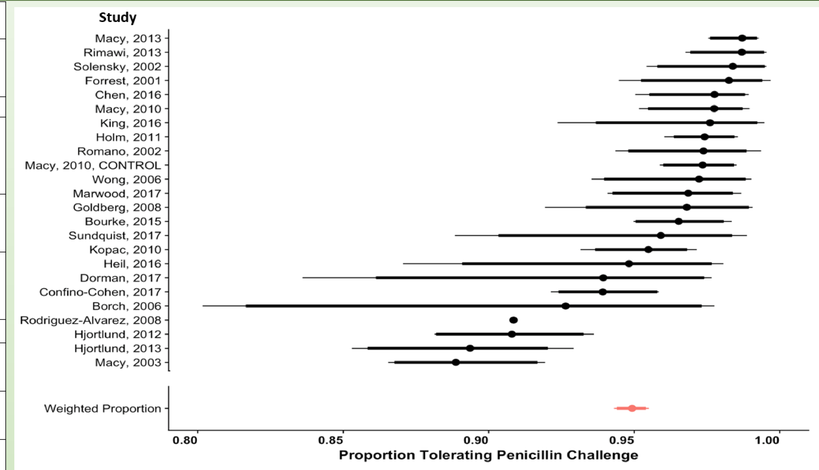
Analysis:

- We calculated the aggregate proportion of patients tolerating a systemic penicillin challenge using a Bayesian beta-binomial model. We included random effects for between-study variability and assumed a non-informative, or "flat" prior probability of penicillin tolerance (prior probability of tolerance ~(Beta(1,1)).

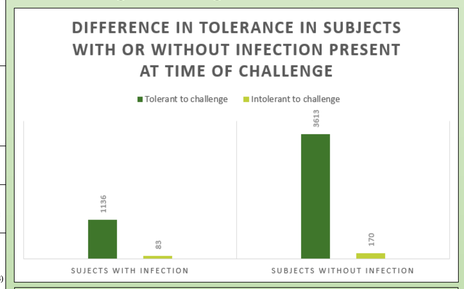
Results

Author, year	Country	Study Design	Total # (n)	Gender, % Female	Age range, years (mean)	Reported penicillin allergy history (n)	Infection present at the time of challenge? Y/N	Drug Provocation Test	N challenged	N not tolerant	Reported reactions after challenge
Borch, et al (2006)	Denmark	Combined cross-sectional case control	96	63%	2-99 (61)	Urticaria (29) Maculopapular rash (34) Angioedema (10) GI symptoms (8) Dyspnea (2) Anaphylaxis (3)	43 Y 53 N	IV PCN G or PO PCN VK challenge, followed by full-dose antibiotics	15	2	NR
Bourke, et al (2015)	Australia	Quasi-experimental study	405	67.10%	15-85 (47.4)	Details not reported, only IMM (151) vs NIM (250)	N	250mg Penicillin VK X 1 dose, followed by specific penicillin initially implicated if different.	375	13	"All were mild cutaneous or subjective reactions"
Chen, et a; (2017)	USA	Quasi-experimental, pre-post cohort design	252	54.40%	16-87 (49.3)	Rash (54) Urticaria / Angioedema (117) Respiratory (47) GI symptoms (16) Cardiovascular symptoms (9) Other/unknown (55)	Y	Amoxicillin 500 mg orally X 1 dose	228	5	1 urticaria 4 not reported
Confino-Cohen, et al (2017)	Israel	Quasi-experimental, prospective cohort	642	51%	0.1-83 (19.9)	Rash (580) Pruritus (151) Dyspnea (23) GI symptoms (13) Angioedema (43) Unknown (202)	N	Graded challenge: 10% therapeutic dose followed by full dose one hour later, followed by 4 days of full dose antibiotics	491	30	Mild rash, pruritus, or abdominal discomfort
Dorman, et al (2017)	USA	Quasi experimental retrospective observational study	32	53%	24-79 (46.9)	Respiratory (3) Hives (11) Angioedema/swelling (6) Rash (19) Hypotension (1) GI symptoms (2) Other / Unknown (5)	Y	IV Penicillins, therapeutic doses	32	3	Throat and ocular pruritus (1) AIN (1) Benign exanthema (1)
Forrest, et al (2001)	Canada	Quasi-experimental, pre-post cohort design	159	NR	NR	NR	Y	Full-dose penicillins, clinically determined	61	0	
Goldberg, et al (2008)	Israel	Prospective open label trial	169	62.70%	5-60 (mean NR, but 90% over the age of 20)	Low blood pressure (4) Dyspnea (13) Rash (113) Pruritus (14) Other / Unknown (57)	N	Oral challenge: penicillin V, or amoxicillin	41	1	Mild cutaneous reaction
Heil, et al (2016)	USA	Quasi-experimental prospective observational study & National Provider Survey	90	69.0%	NR	Rash (16) Hives (28) Swelling (11) Anaphylaxis (14) Unknown (21)	Y	Single test dose (Amoxicillin 250mg PO) or full-dose antibiotics	35	3	Delayed mild rash
Hjortlund, et al (2012)	Denmark	Quasi-experimental, prospective cohort	405	68.60%	16-88 (46)	Urticaria (144) Angioedema (30) Unclassified cutaneous rash (182) Anaphylaxis (9) Unknown (37)	N	IV PCN G, graded challenge Followed by 400mg PO PCN VK Followed by 7 days PO PCN VK800mg Q8H	340	33	Urticaria / angioedema
Hjortlund, et al (2013)	Denmark	Quasi-experimental, prospective cohort	342	70.2%	40-60 (mean NR	Anaphylaxis (11) Angioedema / urticaria (135) Unclassified rash (180) Other cutaneous symptoms (3) Unknown (13)	N	IV PCN G graded challenge Followed by 400mg PO PCN VK Followed by 7 days 800mg TID PCN VK	291	33	Mild cutaneous maculopapular rash (9) Urticaria / angioedema (18) Other, not reported, but notes "no severe reactions were seen"
Holm, et al (2011)	Denmark	Quasi-experimental retrospective study	580	77.0%	13-87 (39)	Skin rash or angioedema	N	IV PCN G graded challenge Followed by full oral provocation dose PCN VK	580	14	Pruritus (7) Rash (4) Swelling of scrotum (1) Subjective swelling of lips and tongue (not objectively confirmed) (1) Flushing of face, swelling of hands (2) Urticaria (5) Sneezing, rhinitis (1)
King, et al (2016)	USA	Quasi experimental retrospective observational study	50	54.0%	Range NR (62)	Rash (17) Hives (9) Anaphylaxis (7) Other / Unknown (17)	Y	Graded challenge, PO amoxicillin up to 250mg Followed by treatment dose penicillin in 37 patients (in whom this was clinically indicated)	50	1	Metallic taste in mouth and throat tightening, but no shortness of breath or wheezing; developed after 1mg amoxicillin PO
Kopac, et al (2010)	Slovenia	Quasi experimental retrospective observational study	606	76%	14-85 (42)	Anaphylaxis (36) Other immediate reaction (243) Delayed reaction (121) Unknown (206)	N	Graded PO challenge with PO PCN VK, amoxicillin, or amoxicillin/clavulonate over 4 hours	426	19	Shortness of breath (1, to amoxicillin) Mild skin symptoms: erythema, urticaria, angioedema (18)
Macy, et al (2003)	USA	Quasi-experimental retrospective cohort study	568	68.80%	0.2-86.1 (39)	Anaphylaxis (32) GI (17) Hives (363) Other rashes (61) Other (30) Unknown (65)	Y	PO PCN VK, amoxicillin, or amoxicillin/clavulonate given at therapeutics doses/courses	568	65	Non-hives rash (47) Hives (2) GI (36) Hives (32) Other reactions: dizziness, wheeze, pruritus without rash (8) "Anaphylaxis" (4); further reviewed, no reaction started within 1 hour, no systemic involvement, no shortness of breath, no faintness, no hypotension, and all resolved spontaneously without treatment.
Macy, et al (2010)	USA	Prospective cohort study	150	69.4%	Range NR(51.8)	NR	N	PO amoxicillin 250 mg, or PO penicillin 500 mg	140	3	Hives (1) Delayed onset rash (2)
Macy, et al, control sample (2010)	USA	Prospective cohort study	307	62.50%	Range NR (43.2)	NR	N	NR	304	7	Hives (1) Delayed rash (1) Subjective itching without rash (5)
Macy, et al (2013)	USA	Prospective case-control, and retrospective population-based cohort study	500	63.40%	1.1-93.4 (40.7)	Non-hive rash (204) Hives / angioedema (169) Anaphylaxis (14) Unknown / Other (113)	N	PO amoxicillin 250mg X 1	495	6	Hives (4) Delayed GI upset (1) Nausea + migraine (1)
Marwood, et al (2017)	Australia	Quasi-experimental, prospective cohort	103	54.0%	19-69 (43)	NR	30 Y 70 N	Graded PO Amoxicillin challenge over 9 days	84	3	Urticarial rash (1) Rash (2) Pruritus (1) Diarrhea (1) Nausea (1)
Rimawi, et al (2013)	USA	Quasi-experimental, pre-post cohort design	146	60.0%	20-80+ (mean NR)	Bronchospasm (23) Urticaria (100) Edema (32) Anaphylaxis (21)	Y	Single test dose PO PCN VK 250mg Followed by full dose antibiotics	146	1	Hives, edema, itching (1)
Rodriguez-Alvarez, et al (2008)	Spain	Quasi-experimental cross-over study	23	48%	0.8-70 (23.4)	Urticaria (7) Other (2) Angioedema (2) Erythema (1) Exanthema (11) Other (2)	N	Oral graded challenge Followed by "home treatment"	21	4	Urticaria (2) Exanthema (1) Erythema of the face and neck (1)
Romano, et al (2002)	Italy	Quasi-experimental, prospective study	259	72.60%	13-84 (37)	Maculopapular rash (173) Urticaria (33) Erythema (22) Angioedema (13) Urticaria/angioedema (13) Local rxn (1) Other manifestations (4)	N	Graded challenge: 1% followed by 10% followed by full dose PO aminopenicillins IV benzylpenicillin (1,000,000 IU) IM benzathine penicillin (1,200,000 IU) or IM piperacillin (1g)	125	3	Maculopapular rash (1); further tested positive for acute EBV Linear IgA bullous dermatosis (1) Oral and vaginal ulceration (1)
Solensky, et al (2002)	USA	Quasi experimental study	53	66%	22-60 (39)	Urticaria/angioedema (25) Pruritic eruption (19) Anaphylaxis (9)	N	10 days PCN VK, X 3 courses	46	0	
Sundquist, et al (2017)	USA	Quasi-experimental prospective cohort	37	51.40%	18-78 (52)	Non-urticarial rash (20) Hives (10) Anaphylaxis (2) Other / Unknown (9)	N	PO amoxicillin 250mg X 1	36	2 (5.6%)	Delayed light headedness, pruritus and sweating (1) Delayed light headedness (1)
Wong, et al (2006)	Canada	Quasi-experimental retrospective cohort	91	36%	0.5-82 (27)	Hives (52) Non-urticarial maculopapular eruption (36) Exfoliation (3) Shortness of breath / wheeze (8) Angioedema of the tongue or face (12) Presyncope (2) GI symptoms (8)	N	7 day graded PO amoxicillin challenge	72	2	Delayed mild generalized urticaria (2)

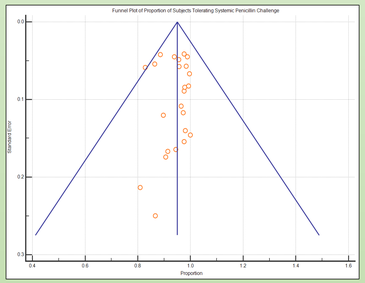
Abbreviations: NR = not reported, PCN G = benzylpenicillin for intravenous administration, PCN VK = phenoxymethylpenicillin for oral administration, PO = administration by mouth, IV = administration intravenously, AIN = acute interstitial nephritis, GI = gastrointestinal



Pooled weighted average tolerance, random effects: 94.89% (CI 92.7, 96.7) I^2 = 89.13%, p<0.001



OR 0.64 (0.49, 0.84)
Difference in proportions is significant
x^2 (1, N=5002) = 10.29, p=0.001



Funnel plot demonstrating significant heterogeneity. Random effects meta-analysis used for relative weighing.

Discussion

Pooled summary estimate of included studies suggests around 95% of patients reporting an allergy to penicillin, who are otherwise at low risk for serious drug reaction, will tolerate systemic administration of penicillin without any notable reaction. The presence of infection at the time of challenge is associated with lower odds of tolerance in our sample, suggesting a role for pre-emptive allergy testing.

- This estimate adds to the previously accepted knowledge that at least 90% of patients reporting an allergy to penicillin are not truly allergic.
- Considering this impressive tolerance, formal evaluation of patients reporting an allergy to penicillin should be systematically performed, ideally pre-emptively.
- Studies evaluating individual patient and clinical characteristics associated with tolerance of penicillin challenge are needed to inform safe, systematic allergy assessment.

Limitations:

- Only studies with English language translations were included in this review
- Due to the nature of our research question, the majority of included articles are quasi-experimental, introducing potential for selection bias and attrition bias affecting internal validity of the included studies.