Addition of probenecid to oral beta-lactam antibiotics: a systematic review and meta-analysis

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**Running Title:** Probenecid and beta-lactam pharmacokinetics

**Abstract**

**Objective:** Explore literature comparing the pharmacokinetic and clinical outcomes from addition of probenecid to oral beta-lactams.

**Data sources:** Medline and EMBASE were searched from inception to December 2021.

**Study eligibility criteria:** All English language studies comparing the addition of probenecid (intervention) to an oral beta-lactam (flucloxacillin, penicillin-V, amoxicillin(+/-clavulanate), cephalexin, cefuroxime-axetil) alone (comparator).

**Risk of bias:** Risk of Bias in Non-randomised studies of interventions (ROBINS-I) and Risk of Bias for Randomised studies 2 (ROB-2) tools were used.

**Methods of data synthesis:** Data on antibiotic therapy, infection diagnosis, primary and secondary outcomes relating to pharmacokinetics and clinical outcomes plus adverse events were extracted and reported descriptively. For a subset of studies comparing treatment failure between probenecid and control groups, meta-analysis was performed.

**Results:** Overall, 18/295 (6%) abstracts screened were included. Populations, methodology, and outcome data were heterogenous. Common populations included healthy volunteer (9/18;50%) and gonococcal infection (6/18;33%). Most studies were cross-over trials (11/18;61%) or parallel arm randomised trial (4/18;22%).

Where pharmacokinetic analyses were performed, addition of probenecid to oral beta-lactams increased total AUC (7/7;100­%), peak observed concentration (Cmax,5/8;63%), and serum half-life (t1/2,6/8;75%). Probenecid improved PTA (2/2;100%).

Meta-analysis of 3105 (2258 intervention, 847 control) patients treated for gonococcal disease demonstrated a relative risk of treatment failure in the random effects model of 0.33 (95%CI:0.20-0.55; *I2*=7%), favouring probenecid.

**Conclusion:** Probenecid boosted beta-lactam therapy is associated with improved outcomes in gonococcal disease. Pharmacokinetic data suggest that probenecid boosted oral beta-lactam therapy may have a broader application, but appropriately powered mechanistic and efficacy studies are required.

**Abstract: 250**

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**Introduction**

Probenecid, p-(di-*n*-propylsulfamyl)-benzoic acid, was developed in 1949 with the purpose of decreasing the renal clearance of penicillin.1 Its mechanism of action is through competitive inhibition of organic anion transporters, which are responsible excretion of organic agents, such as penicillin.2 Reduction in renal clearance of penicillin with probenecid demonstrated significant increases in serum exposure, meaning that lower doses of drug were required for similar pharmacokinetic-pharmacodynamic (PK-PD) target attainment. Probenecid’s influence on penicillin clearance became mainly academic in the post-war era as the capability to produce more diverse, cheaper, and safer beta-lactam antibiotics rapidly expanded.1 Probenecid remains a recommended adjunct in the management of some sexually transmitted infections to support therapeutic target attainment in compartments, such as cerebrospinal fluid in neurosyphilis.3 However, its potential important and broader role in preserving the effectiveness of beta-lactams through the optimisation of beta-lactam PK and dosing schedules needs to be considered as well as possible adverse events associated with its use, such as nausea and unfavourable drug-drug interactions.

Globally, the WHO Access, Watch, and Restrict (AWaRe) criteria require narrow spectrum antimicrobials, such as the penicillins, to be available in appropriate type, dose, and duration to treat common infections.4 With increasing drug-resistance within common causative organisms, such as in Streptococci, new methods to optimise the delivery of *Access* agents and protect the use of broader *Watch* and *Reserve* antimicrobials are required.4,5

It is not always possible to administer higher doses of an oral antibiotic to achieve an optimal PK-PD profile. In some instances, oral drug absorption or gastrointestinal side effects are associated with high doses and limit escalation of therapy. In other situations, augmented renal clearance may make achieving optimal drug exposure difficult. Some agents are not licenced for use at oral doses that would be required to obtain acceptable PK-PD target attainment. Opportunities to deliver oral narrow-spectrum agents in an optimised format may offer an attractive opportunity within local antimicrobial stewardship agendas and support the avoidance of prolonged courses of intravenous treatment in certain infections.6,7

We explored current and historical literature that compared the use of probenecid with an oral beta-lactam antibiotic versus the beta-lactam antibiotic alone describing it impact on PK, clinic outcomes, and reported adverse events. The aim was to describe the current literature in support of this approach and identify gaps in knowledge that can be addressed by future mechanistic and efficacy-based research.

**Method**

*Search criteria*

We performed a search of MEDLINE and EMBASE using the search terms outlined in ***supplementary table 1***. Studies in English reporting direct comparison of probenecid plus an oral beta-lactam versus the oral beta-lactam alone in human subjects were included. Common oral beta-lactam antibiotics used in the UK were selected for inclusion. These were flucloxacillin, penicillin-V, amoxicillin, ampicillin, amoxicillin-clavulinate, cephalexin, and cefuroxime axetil. Only full text, original research articles comparing the addition of probenecid to the same oral beta-lactam antibiotic were included. Articles were required to describe PK-PD, microbiology, or adverse event outcomes to be included. Anything published before December 2021 was included and no prior time limit was set. Studies were excluded if they were not in English, were reviews and letters, compared different antimicrobial agents or routes of delivery, or reported on non-human subjects. This review was registered on the PROSPERO database prior to data extraction (registration number: CRD42021298765).

*Study selection*

Specific literature review software (Covidence, Australia) was used. Two authors (TMR and RW) independently reviewed abstracts and full texts against inclusion and exclusion criteria. Articles that met screening and eligibility checks were carried forwards for full text review. References of published literature were also reviewed to identify further full texts for inclusion.

*Data extraction*

Data were extracted by one researcher (TMR) with cross-checking independently performed by a second author (RW or MG). Data extracted included publication details (authors, journal, year of publication), study details (participants, study design, intervention, control, dosing schedules), primary and secondary outcomes (including PK data and/or clinical outcome), and reported adverse events / toxicity.

*Risk of bias*

Risk of bias for individual studies were assessed in line with Cochrane recommendations. For non-randomised studies the Risk of Bias in Non-randomised studies of interventions (ROBINS-I) assessment tool was used8. For randomised studies, the Risk of Bias for Randomised studies 2 (ROB-2) tool was used.9 Risk of bias was assessed by two reviewers (TMR & RW) independently of each other. Where disagreement in domain scoring occurred, a third reviewer assessed the study and differences were discussed to reach consensus.

*Data analysis*

Data were analysed descriptively in line with the aims of this review. For a subset of studies comparing treatment failure between probenecid and control groups, meta-analysis was performed using “metabin” function from the “meta” package (version 4.11-0) in R (version 3.5.1).9 Treatment failure was defined in these studies as microbiological failure, with growth of *Neisseria gonorrhoea* during follow-up visit after treatment and not associated with self-reported history of re-exposure. Study findings were displayed in forest plots demonstrating the relative risk determined using the Mantel-Haenszel method. Heterogeneity was visually assessed using funnel plots and the *I2* statistic. As study quality were expected to be highly variable, an *a priori* decision was made to proceed with meta-analysis as part of the subgroup analysis despite an expected moderate to high risk of bias within studies. Bias plots were generated using the “robvis” package in R.9

**Results**

*Study selection*

**Figure 1** outlines the study selection process. In total, 340 references were identified with 45 (13%) duplicates removed. Of the 295 titles and abstracts screened, 100 (34%) were carried forwards for full text review. On full text review, a further 81/100 (81%) were excluded. Common reasons for exclusion were use of wrong intervention / comparator agent (56/81; 69%) and wrong outcome measures described (9/81; 11%). One manuscript was not accessible.10 Therefore, 18/295 (6%) manuscripts were included in the review.11–28

*Study characteristics*

**Table 1** summarises studies included. Studies reported from 1969 to 2021. Populations, methodology, and outcome measures were heterogenous. Most studies were healthy volunteer12,14,16,19,20,23–25,27 (9/18; 50%) or in patients with gonococcal infection13,15,17,21,22,26 (6/18; 33%). Additional studies reported on patients with bronchiectasis (1/18; 6%),11 biliary pathology (1/18; 6%),18 and invasive *Staphylococcus aureus* infection (1/18; 6%).28 Cross-over trials (11/18; 61%), parallel arm randomised trials (4/18; 22%), observational (2/18; 11%) and dose escalation (1/18; 6%) studies were reported.

Studies compared different oral beta-lactam antibiotics with and without probenecid. These were ampicillin (3/18; 17%), amoxicillin (6/18; 33%), amoxicillin-clavulanate (1/18; 6%), flucloxacillin (2/18; 11%), cephalexin (4/18; 22%), cefuroxime axetil (2/18; 11%), and penicillin-V (1/18; 6%). Doses of beta-lactam and frequency of treatment varied between study. Most studies described single doses of beta-lactam with or without probenecid (15/18; 83%). Probenecid dosing varied between 250 and 1000 mg per single dose in these studies. Primary outcome measures differed between studies with the effect of probenecid on oral beta-lactam PK reported in 12/18 (67%) studies and treatment outcomes (failure of therapy) reported in 6/18 (33%) studies.

*Risk of bias in studies*

**Supplementary figure 1** summarises the risk of bias for both randomised and non-randomised studies included within this review. Overall, there was a moderate to high risk of bias in most studies with low overall risk in 2/18 (11%) studies only.

*Studies reporting beta-lactam pharmacokinetics*

Despite variable beta-lactam choice and dose, methods of beta-lactam quantification, and methods of data analysis, common observations were present. Of 12 studies reporting the effect of probenecid on beta-lactam PK as a primary outcome, 7/12 (58%) described the influence on AUC, 8/12 (67%) serum half-life (t1/2), and 8/12 (67%) peak observed serum concentration (Cmax). Two of 12 studies (17%) reported the use of Monte Carlo simulation to estimate PTA. Addition of probenecid to oral beta-lactam antibiotics increased total AUC in 7/7 (100%) studies reporting it. Beta-lactam Cmax was significantly increased in 5/8 (63%) and t1/2, 6/8 (75%) of studies reporting these variables. Both studies assessing PTA (2/2; 100%) demonstrated a significant increase in target attainment with the addition of probenecid to beta-lactam therapy.

*Studies reporting treatment failure*

Of the 6/18 (33%) studies reporting on treatment failure as a primary outcome, 4/6 (67%) were included in a meta-analysis comparing the addition of probenecid to an oral beta-lactam antibiotic of the same dose on treatment outcome (**Figure 2**).15,17,21,26 One study (17%) could not be included as different doses of ampicillin were used in the intervention and control arms.13 A further study (1/6; 17%) could not be included due to different dosing schedules between intervention and control arms.22 All four included studies reported on the outcome of treating gonococcal disease with microbiological failure at follow-up used to define treatment failure. Three (75%) were randomised studies with one (25%) observational in design. They contained seven direct comparisons of addition of probenecid to an oral beta-lactam antibiotic of fixed dose on treatment outcome in 3105 (2258 intervention and 847 control) patients. The relative risk of treatment failure in the random effects model was 0.33 (95%CI 0.20-0.55; *I2* = 7%), favouring the addition of probenecid to oral beta-lactam regimes.

*Side effects and toxicity*

The assessment of side effects / toxicity was reported in 11/18 (61%) studies. Of these, 4/11 (36%) observed side effects, with 7/11 (64%) not reporting any observed adverse events. One randomised study identified a higher rate of reported nausea for 1g cefuroxime axetil with 1g probenecid (7/57; 12%) versus 1g cefuroxime axetil alone (1/52; 2%).17 Within this study, rates of vomiting and diarrhoea were similar. A further study highlighted an increase in observed reports of nausea and dizziness associated with 1g BD probenecid in patients receiving 7 days of treatment for furunculosis.28 Unfortunately, the observed rate was not quantified by the authors. Allen and colleagues reported 1 case of nausea associated with an arm containing 1g BD of probenecid in their study of amoxicillin pharmacokinetics in patients with bronchiectasis.11 The final study to observe side effects reported six patients with nausea from their entire cohort. The authors do not differentiate between those receiving beta-lactam antibiotic alone versus beta-lactam antibiotic with probenecid.15 PK data for probenecid and or beta-lactam antbiotics was not provided or not available in a way that allowed evaluation of the impact of drug-exposure on these reported outcomes.

**Discussion**

This review highlights the current paucity of evidence for the use of probenecid to optimise the delivery of oral beta-lactam antibiotics. Current data are heterogenous, use historical methods of drug quantification, and focus predominantly on the management of gonococcal disease. Current evidence suggests that addition of probenecid to oral beta-lactam therapy reduces microbiological treatment failures in gonococcal disease compared to use of single doses of an oral beta-lactam antibiotic alone. In addition, the influence of probenecid on oral beta-lactam PK leads to potentially favourable drug exposures that may enhance target attainment for other infective aetiologies requiring longer courses of antimicrobial therapy, including *Staphylococcus aureus* infection.

Beta-lactam antibiotics exhibit time-dependent mechanisms of action. In the late 20th and early 21st centuries, optimal PK-PD targets for beta-lactams have been explored and defined. The time the free (unbound) concentration of beta-lactam spends above an organisms MIC (*f*T>MIC) best describes beta-lactam PK-PD.29 Traditionally, targets of greater than 40-50% *f*T>MIC are targeted with evidence that attainment of this target leads to improved patient outcomes.29 For some infections, such as those caused by Gram positive bacteria, lower *fT>*MIC may be recommended. However, to prevent the development of drug-resistance for *Pseudomonas aeruginosa* during therapy, targets between 100% *f*T>MIC and 100% *f*T>4-6xMIC have been explored.30–32 To enhance the efficacy of beta-lactam antibiotics, different approaches have been trialled including prolonged and continuous infusions in patients with variable PK.33–35 The benefit of higher doses of oral penicillin for shorter durations have also been demonstrated in conditions such as streptococcal throat infection.36 Probenecid’s ability to potentially prolong terminal t1/2, and increase Cmax and AUC of both oral and intravenous agents suggests an alternative option to increasing antimicrobial doses or frequency when optimising PK-PD targets. Everts and colleagues demonstrated significant increases in the probability of target attainment for the treatment of *Staphylococcus aureus* using oral flucloxacillin co-administered with probenecid compared to oral flucloxacillin alone in healthy volunteers.23 These pre-clinical data are further supported by observational studies reporting favourable outcomes for the management of staphylococcal infections using flucloxacillin with probenecid.37 Furthermore, Grayson and colleagues demonstrated favourable clinical outcomes with intravenous cefazolin plus probenecid compared to ceftriaxone for the treatment of moderate to severe cellulitis as part of a third-generation cephalosporin-sparing regimen.38

*Current limitations and future steps*

Despite emerging observational data supporting the safety and efficacy of probenecid boosted oral beta-lactam therapy, several mechanistic and efficacy questions remain. Current data is limited by the relatively small sample sizes employed in most studies. No experimental data comparing oral beta-lactams with and without probenecid have been reported outside of its use in gonococcal disease. Historical analysis on beta-lactam PK often determined total antimicrobial exposure from single drug doses and used old methods of quantification, such as tube dilution methods. These methods were often open to wide variation and make direct comparison between studies challenging. Furthermore, the use of total drug concentration does not allow for the active component (free drug concentration) to be described or understood, meaning that the true impact of probenecid on free antibiotic concentration remains to be defined in many cases. Finally, probenecid is know to interact with a number of common medications seen in multi-morbid patients, including paracetamol, non-steroidal anti-inflammatories, antipsychotic medications, and immunosuppressents.39 Consideration of these factors on treatment selection and outcomes is lacking from current data.

Future work should focus on characterisation of the direct efficacy of addition of probenecid to common oral beta-lactam antimicrobial dosing regimens. These studies could include the mechanistic characterisation of probenecid’s influence on free chemically active drug and include assessment of clearance, plasma protein binding, and target site concentration attainment. As well as demonstrating enhanced antimicrobial PK using probenecid, an impact on antimicrobial PD, clinical outcomes, and toxicity must be clearly demonstrated. Future work should include the assessment and definition of probenecid PK-PD. With improved opportunities to provide therapeutic drug monitoring of both oral beta-lactams and probenecid,40,41 this will further enhance the clinical acceptability of PK manipulation with probenecid and address concerns surrounding potential toxicity, which has not been reported in studies to date.

**Conclusion**

Probenecid is associated with improved microbiological cure at follow-up when added to oral beta-lactam regimens for the treatment of gonococcal disease. Pre-clinical and observational data suggest that probenecid boosted oral beta-lactam therapy may have a broader application in the future. To define the potential role of probenecid boosted oral beta-lactam regimes, appropriately powered mechanistic and efficacy-based studies to facilitate direct comparison should be conducted.

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**Transparancy declaration**

TMR & MG developed the concept and methodology for the review. TMR, RW, and MG undertook data extraction and reviewing. All authors contributed significantly to data interpretation. TMR drafted the initial manuscript. All authors contributed significantly to the revision of the manuscript and finalisation for submission.

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**References:**

1. Robbins N, Koch SE, Tranter M, *et al*. The History and Future of Probenecid. *Cardiovasc Toxicol* 2012; **12**: 1–9.

2. Maeda K, Tian Y, Fujita T, *et al.* Inhibitory effects of p-aminohippurate and probenecid on the renal clearance of adefovir and benzylpenicillin as probe drugs for organic anion transporter (OAT) 1 and OAT3 in humans. *Eur J Pharm Sci* 2014; **59**: 94–103.

3. Frieden TR, Harold Jaffe DW, Rasmussen SA, *et al.* Sexually Transmitted Diseases Treatment Guidelines*. MMWR*. 2015. https://www.cdc.gov/mmwr/pdf/rr/rr6403.pdf

4. Sharland M, Pulcini C, Harbarth S, *et al.* Classifying antibiotics in the WHO Essential Medicines List for optimal use-be AWaRe. *Lancet Infect Dis* 2018; **18**: 18–20.

5. World Health Organisation. *GLASS | Global Antimicrobial Resistance Surveillance System (GLASS)*. World Health Organization; 2020. https://apps.who.int/iris/handle/10665/3320816. Seaton RA, Ritchie ND, Robb F, *et al*. From ‘OPAT’ to ‘COpAT’: implications of the OVIVA study for ambulatory management of bone and joint infection. *J Antimicrob Chemother* 2019; **74**: 2119–21.

7. Gilchrist M, Seaton RA. Outpatient parenteral antimicrobial therapy and antimicrobial stewardship: challenges and checklists. *J Antimicrob Chemother*. *J Antimicrob Chemother* 2015. **70**:965-70

8. Sterne JA, Hernán MA, Reeves BC, *et al.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016: **12**: i4919.

9. Sterne JAC, Savović J, Page MJ, *et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019 **28**: l4898.

10. Jacoby A, Pollock J, Boghosian V Oral penicillin with and without benemid in the treatment of gonorrhea. *Am J Syph Gonorrhea Vener Dis* 1954; **38**: 478–9.

11. Allen MB, Fitzpatrick RW, Barratt A, *et al*. The use of probenecid to increase the serum amoxycillin levels in patients with bronchiectasis. *Respir Med* 1990; **84**: 143–6.

12. Barbhaiya R, Thin RN, Turner P, *et al*. Clinical pharmacological studies of amoxycillin: Effect of probenecid. *Br J Vener Dis* 1979; **55**: 211–3.

13. Karney WW, Turck M, Holmes KK. Single-Dose Oral Therapy for Uncomplicated Gonorrhea: Comparison of Amoxicillin and Ampicillin Given with and without Probenecid. *J Infect Dis* 1974; **129**: S250–3.

14. Meyers BR, Kaplan K, Weinstein L. Cephalexin: Microbiological effects and pharmacologic parameters in man. *Clin Pharmacol Ther* 1969; **10**: 810–6.

15. Mitchell RW, Robson HG. Comparison of amoxicillin and ampicillin in single dose oral treatment of males with gonococcal urethritis. *Can Med Assoc J* 1974; **111**: 1198–200.

16. Paulsen O, Hoglund P, Schalen C. Pharmacokinetic comparison of two models of endocarditis prophylaxis with amoxycillin. *Scand J Infect Dis* 1989; **21**: 669–73.

17. Reichman RC, Nolte FS, Wolinsky SM, *et al*. Single-dose Cefuroxime Axetil in the Treatment of Uncomplicated Gonorrhea: A Controlled Trial. *Sex Transm Dis* 1985; **12**: 184–7.

18. Sales JEL, Sutcliffe M, O’grady F. Cephalexin Levels in Human Bile in Presence of Biliary Tract Disease. *Br Med J* 1972; **3**: 441–3.

19. Shanson DC, Mcnabb R, Hajipieris P. The effect of probenecid on serum amoxycillin concentrations up to 18 hours after a single 3 g oral dose of amoxycillin: Possible implications for preventing endocarditis. *J Antimicrob Chemother* 1984; **13**: 629–32.

20. Staniforth DH, Jackson D, Clarke HL, *et al*. Amoxycillin/clavulanic acid: The effect of probenecid. *J Antimicrob Chemother* 1983; **12**: 273–5.

21. Bro-Jorgensen A, Jensen T. Single-dose oral treatment of gonorrhea in men and women, using ampicillin alone and combined with probenecid. *Br J Vener Dis* 1971; **47**: 443–7.

22. Eriksson G. Ampicillin serum levels and treatment results in gonorrhoea. *Br J Vener Dis* 1973; **49**: 353–7.

23. Everts RJ, Begg R, Gardiner SJ, *et al.* Probenecid and food effects on flucloxacillin pharmacokinetics and pharmacodynamics in healthy volunteers. *J Infect* 2020; **80**: 42–53.

24. Everts RJ, Gardiner SJ, Zhang M, *et al.* Probenecid effects on cephalexin pharmacokinetics and pharmacodynamics in healthy volunteers. *J Infect* 2021; **83**: 182–9.

25. Frisk AR, Diding N, Wallmark G. Influence of probenecid on serum penicillin concentration after oral administration of penicillin. *Scand J Clin Lab Invest* 1952; **4**: 83–8.

26. Gottlieb A, Mills J. Cefuroxime axetil for treatment of uncomplicated gonorrhea. *Antimicrob Agents Chemother* 1986; **30**: 333–4.

27. Gower PE, Dash CH. Cephalexin: human studies of absorption and excretion of a new cephalosporin antibiotic. *Br J Pharmacol* 1969; **37**: 738–47.

28. Hedström SÅ, Kahlmeter G. Dicloxacillin and Flucloxacillin Twice Daily with Probenecid in Staphylococcal Infections: A Clinical and Pharmakokinetic Evaluation. *Scand J Infect Dis* 1980; **12**: 221–5.

29. Roberts JA, Norris R, Paterson DL, *et al*. Therapeutic drug monitoring of antimicrobials. *Br J Clin Pharmacol* 2012; **73**: 27–36.

30. Bilgrami I, Roberts JA, Wallis SC, *et al.* Meropenem Dosing in Critically Ill Patients with Sepsis Receiving High-Volume Continuous Venovenous Hemofiltration. *Antimicrob Agents Chemother* 2010; **54**: 2974–8.

31. Mouton JW, Den Hollander JG. Killing of Pseudomonas aeruginosa during continuous and intermittent infusion of ceftazidime in an in vitro pharmacokinetic model. *Antimicrob Agents Chemother* 1994; **38**: 931–6.

32. Tam VH, Schilling AN, Neshat S, *et al*. Optimization of meropenem minimum concentration/MIC ratio to suppress in vitro resistance of Pseudomonas aeruginosa. *Antimicrob Agents Chemother* 2005; **49**: 4920–7.

33. Roberts JA, Lipman J, Blot S, *et al*. Better outcomes through continuous infusion of time-dependent antibiotics to critically ill patients? *Curr Opin Crit Care* 2008; **14**: 390–6.

34. Roberts JA, Abdul-Aziz M-H, Davis JS, *et al.* Continuous versus Intermittent β-Lactam Infusion in Severe Sepsis. A Meta-analysis of Individual Patient Data from Randomized Trials. *Am J Respir Crit Care Med* 2016; **194**: 681–91.

35. Osthoff M, Siegemund M, Balestra G, *et al*. Prolonged administration of β-lactam antibiotics - a comprehensive review and critical appraisal. *Swiss Med Wkly* 2016; **146**: w14368.

36. Skoog Ståhlgren G, Tyrstrup M, Edlund C, *et al.* Penicillin V four times daily for five days versus three times daily for 10 days in patients with pharyngotonsillitis caused by group A streptococci: randomised controlled, open label, non-inferiority study. *BMJ* 2019: **4**: l5337.

37. Drennan PG, Green JK, Gardiner SJ, *et al.* Population pharmacokinetics of free flucloxacillin in patients treated with oral flucloxacillin plus probenecid. *Br J Clin Pharmacol* 2021:**87:**14887.

38. Grayson ML, Mcdonald M, Gibson K, *et al.* *Once-Daily Intravenous Cefazolin Plus Oral Probenecid Is Equivalent to Once-Daily Intravenous Ceftriaxone Plus Oral Placebo for the Treatment of Moderate-to-Severe Cellulitis in Adults*. *Clin Infect DIs* 2002. **34**:1440-8

39. Cunningham RF, Israili ZH, Dayton PG. Clinical Pharmacokinetics of Probenecid. *Clin Pharmacokinet* 1981; **6**: 135–51.

40. Sime FB, Roberts MS, Peake SL,*et al*. Does beta-lactam pharmacokinetic variability in critically III patients justify therapeutic drug monitoring? A systematic review. *Ann Intensive Care* 2012; **2**: 35.

41. Rawson TM, Gowers SAN, Freeman DME, *et al.* Microneedle biosensors for real-time , minimally invasive drug monitoring of phenoxymethylpenicillin : a first-in-human evaluation in healthy volunteers. *Lancet Digit Heal* 2019. **7,** E335-E343

**Figure 1.** PRISMA diagram summarising screening and eligibility checking process





**Table 1.** Summary of studies comparing the addition of probenecid to an oral beta-lactam antibiotic included in the final review

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Paper** | **Population** | **Design** | **Intervention** | **Control** | **Microbiological outcome** | **Pharmacokinetic data** | **Adverse events** |
| Allen et al 111990 | 6 patients (4 female) with stable bronchiectasis.Median age 53.5 years. | Randomised cross-over of 3 regimens  | Amoxicillin 1g BD plus probenecid 500mg QDS ORAmoxicillin 1g BD plus probenecid 1g BD  | High dose amoxicillin 3g BD plus placebo | Nil | Probenecid reduced amoxicillin clearance to 1/3 of that with the placebo. No influence on Cmax or t1/2 identified. | 1 patient reported nausea with probenecid 1g BD arm.  |
| Barbhaiya et al 121979 | 8 healthy volunteers. 22-26 years old. | Cross-over study | Amoxicillin 3g with 1g probenecid | Amoxicillin 3g alone | Nil | Greater peak amoxicillin concentration and larger AUC with probenecid. | N/A |
| Bro-Jorgensen & Jensen 211971 | 1915 men and 921 females with uncomplicated gonorrhoea  | Observational study comparing 4-regimes | Ampicillin 1g plus 1g probenecidOr Ampicillin 2g plus 1g probenecid | Ampicillin 1g Or Ampicillin 2g  | *Microbiological failure within 14 days of treatment.*Ampicillin 1g treatment failure 10.6% malesAmpicillin 2g treatment failure 6.5% in malesAmpicillin plus probenecid failure rate 1.9% both schedules in males. No significant difference in treatment outcomes in females. |  | Nil observed. |
| Eriksson 221973 | 96 out-patients with uncomplicated gonorrhoea | Observational study | Ampicillin 2g plus 1g probenecid | Ampicillin 2g in divided dose 5-hrs apart | *Microbiological failure identified during two follow up visits.*Ampicillin plus probenecid treatment failure 3/24 (13%). Ampicillin 2/72 (3%) with 3/72 (4%) in this arm also lost to follow up. | No correlation between serum concentration and recurrent positive culture. | N/A |
| Everts et al 232020 | 11 healthy volunteers (7 female, 4 male) | Cross-over study | Flucloxacillin 1000 mg plus probenecid 500 mg  | Flucloxacillin 1000 mg | Nil | Probenecid increased the free flucloxacillin AUC. Reduced clearance by approximately 53-55%. 2-5 fold increase in flucloxacillin PK-PD target attainment. | Nil observed. |
| Everts et al 242021 | 11 healthy volunteers (7 female, 4 male) | Cross-over study | Cephalexin 1g plus probenecid 500mg  | Cephalexin 1g  | Nil | Probenecid increased cephalexin AUC, Cmax, and t1/2. Enhanced PTA for Staph aureus. | Nil observed.  |
| Frisk et al 251952 | 14 healthy volunteers | Dose escalation study | Penicillin 500,000 units with escalating dose of probenecid from 0.25mg to 1g | Penicillin 500mg alone | Nil | There is a linear relationship between PBC dose and increase in plasma penicillin concentration in the PBC dosing range of 0.25-1g of PBC. | Nil observed. |
| Gottlieb & Mills 261986 | 65 men who have sex with men with suspected gonorrhoea | Randomised, parallel arms study | Cefuroxime 1g plus probenecid 1g | Cefuroxime 1g | *Microbiological failure within 4-7 days of treatment.*Probenecid arm had 1/36 failures at 4-7 days. Control arm had 3/29 failures. |  Nil | N/A |
| Gower & Dash 271969 | 6 health volunteers | Cross-over study | Cephalexin 1g QDS plus probenecid 500mg QDS | Cephalexin 1g QDS | Nil | Probenecid increased peak cephalexin concentration and serum t1/2. Probenecid significantly reduced urinary excretion of cephalexin | Nil observed.  |
| Hedstrom & Kahlmeter 281980 | 6 patients with *Staphylococcus aureus* infection (4 male, 2 female) | Cross-over study | Flucloxacillin 1g BD plus probenecid 1g BD | Flucloxacillin 1g BD | Nil | Probenecid increased flucloxacillin t1/2 and doubled AUC in the central compartment.  | Nausea & dizziness reported in “a few” patients receiving probenecid 1g BD in a separate observational phase of the study in 35 patients with furunculosis, 1/35 patients reported urticaria and 4/35 exanthem. |
| Karney et al 131974 | 155 patients with anogenital gonorrhoea (80 male, 75 female) | Randomised, double blind, parallel arms study | Ampicillin 3.5g plus 1g probenecid | Ampicillin 3g | *Microbiological failure within 3-7 days of treatment.*Probenecid arm had less failures at 14 days with 1/60 (2%) vs. 8/90 (9%) in control. |  Nil | N/A |
| Meyers et al 141969 | 10 healthy volunteers | Cross-over study | Cephalexin 500mg plus 500mg probenecid | Cephalexin 500mg  | Nil | Probenecid increased the serum t1/2 of cephalexin. | N/A |
| Mitchell & Robson 151974 | 102 males with urethral discharge  | Randomised, parallel arms study | Amoxicillin 2g plus probenecid 1g | Amoxicillin 2g | *Microbiological failure within 28 days of treatment.*Cure with probenecid 50/52 (98%), amoxicillin alone 39/45 (89%) |  Nil | 6 patients reported gastrointestinal side effects. Unclear whether associated with probenecid arm. |
| Paulsen et al 161989 | 12 healthy volunteers (7 male, 5 female) | Randomised cross-over study | Amoxicillin 1g plus probenecid 1g | Amoxicillin 1gAnd Amoxicillin 3g | Nil | Probenecid increased amoxicillin t1/2 and peak concentration. This led to a doubling of the AUC. No significant difference in PK parameters when compared to 3g amoxicillin. | N/A |
| Reichman et al 171985 | 124 patients with uncomplicated gonorrhoea (20 female, 104 male) | Blinded, randomised, parallel arms study | Cefuroxime axetil 1g plus probenecid 1g | Cefuroxime axetil 1g | *Microbiological failure within 4-7 days of treatment.*Cure within probenecid arm in 55/56 (98%) versus 50/51 (98%) in control arm. | Nil | Nausea (7/57 vs. 1/52) was more predominant with probenecid. Vomiting (2/57 vs. 1/52) & diarrhoea (6/57 vs. 7/52) were similar. |
| Sales et al 181972 | 9 patients with T-tubes in the CBD post cholecystectomy | Cross-over study | Cephalexin 1g plus probenecid 500mg (n = 5 patients) | Cephalexin 1g | Nil | Probenecid led to significant increase in observed bile cephalexin concentration.  | N/A |
| Shanson et al 191984 | 10 healthy volunteers | Randomised cross-over study | Amoxicillin 3g plus probenecid 1g | Amoxicillin 3g | Nil | Serum concentration was significantly higher at all collected time points over 18-hours with probenecid | Nil observed. |
| Staniforth et al 201983 | 16 healthy volunteers | Cross-over study | Amoxicillin 500mg plus probenecid 1gAnd Augmentin 750mg plus probenecid 1g | Amoxicillin 500mg And Augmentin 750mg | Nil | Probenecid had no effect on clavulanic acid PK. A small change in renal clearance was noted. Amoxicillin AUC, Cmax, and t1/2 were increased. | Nil observed.  |

**Legend:** BD = 12-hourly dosing, QDS = 6-hourly dosing, Cmax = maximum observed concentration (mg/L), t1/2 = serum half-life, AUC = area under the concentration time curve, PTA = probability of target attainment.

**Figure 2.** Meta-analysis of the relative risk of microbiological failure of treatment for gonococcal disease for probenecid boosted oral beta-lactams versus oral beta-lactam antibiotic alone



**Legend:** UCG = uncomplicated gonococcal disease; UD = urethral discharge of presumed gonococcal disease; G = gonococcal disease (complicated and uncomplicated); RR = relative risk; I2 = dispersion of effect size within the meta-analysis; τ2 = estimated amount of total heterogeneity