Doxycycline Individual Level Harms – Antimicrobial Resistance

Doxycycline use and antimicrobial resistance search strategy:

PubMed search was conducted of English language articles from January 1, 1990 to February 13, 2023 using the following search terms:

- Long term use AND doxycycline AND antimicrobial resistance
- Long term use of doxycycline AND antimicrobial resistance
- Doxycycline resistance AND staphylococcus aureus
- Doxycycline resistance AND streptococcus pneumoniae
- Doxycycline resistance AND enteric pathogens
- Doxycycline resistance AND shigella
- Doxycycline resistance AND salmonella
- Doxycycline resistance AND Mycoplasma genitalium
- Doxycycline resistance AND malaria prophylaxis
- Doxycycline resistance AND gonorrhea or Neisseria gonorrhoeae
- Doxycycline resistance AND chlamydia or chlamydia trachomatis
- Doxycycline resistance AND treponema pallidum
- Doxycycline resistance AND syphilis

Inclusion criteria: English language; the dose of doxycycline in the population studied was at least 100mg a day and not under 100mg a day; the population studied experienced “long term” doxycycline use (either using this term or by documenting doxycycline use was measured in months); the study outcomes included antimicrobial susceptibility or resistance of bacteria in the study population.

Acne patient studies

Citation	Summary of Findings	Number of Particpants (Studies)	Quality of evidence
Moon SH(1), Roh HS, Kim YH, Kim JE, Ko JY, Ro YS. J Dermatol. 2012 Oct;39(10):833-7. doi: 10.1111/j.1346-8138.2012.01626.x. Epub 2012 Jul 11. Antibiotic resistance of microbial strains isolated from Korean acne patients. Antibiotic resistance of microbial strains isolated from Korean acne patients.	Bacteria were isolated from 20-28% of the patients. Only the bacteria from patients in the treatment group were resistant to antibiotics, whereas none of the bacteria were resistant to antibiotics in the non-treatment group. The untreated group (doxy) was small, n=4 (Proprionibacterium acnes) and n=7 (Staphylococcus epidermis). Staphylococcus epidermis: Resistance not related to treatment history p= 0.23 Doxycycline DOSE taken by patients: no details on mg or length of treatment aside from “long-term” treatment being of interest	100 patients with acne yielded: 30 P acnes strains, 36 S epi colonies, 8 S aureus colonies.	Low
Tan HH(1), Goh CL, Yeo MG, Tan MLAntibiotic sensitivity of Propionibacterium acnes isolates from patients with acne vulgaris in a tertiary dermatological referral centre in Singapore. . Ann Acad Med Singap. 2001 Jan;30(1):22-5.	In patients who had never been on antibiotics, there were no resistant isolates of Proprionibacterium acnes. In patients who had been on short-term antibiotics (between 6 to 18 weeks), there were 2 resistant strains among the 34 isolates (6.25%); in patients who had been on antibiotics for longer periods, there were 11 resistant strains among the 51 isolates (21.6%). [0-6-22% across the 3 groups was significant] The differences in the rates of isolation of resistant strains between patients who had not been on antibiotics to those that had been on long-term antibiotics were statistically significant (P = 0.015). There was also a significant difference in isolation of resistant strains from those on short-term antibiotics compared to those who had been on long-term antibiotics (P = 0.036). Resistance to erythromycin was most commonly encountered. Most of the erythromycin-resistant strains also showed cross-resistance to clindamycin. The average MICs to antibiotics such as minocycline, erythromycin and clindamycin in those on long-term antibiotics were significantly higher when compared to patients who had not been on antibiotics. FOR DOXY: they looked at MICs which followed the same pattern of MIC increasing from Group A to B to C but was not significant. DOSE: no standard regimen reported	150 patients; results indicate 85 isolates; 6-18 weeks duration vs 24 to 52 weeks of Abx	Low
Legiawati L, Halim PA, Fitriani M, Hikmahrachim HG, Lim HW. Microbiomes in Acne Vulgaris and Their Susceptibility to Antibiotics in Indonesia: A Systematic Review and Meta-Analysis. Antibiotics (Basel). 2023 Jan 11;12(1):145. doi: 10.3390/antibiotics12010145.	Limited to Indonesia. C. acnes and S. epidermidis was most common from acne vulgaris lesions. 11/16 included studies examined AMR in isolates: 24-28% of isolates were TET-R. No causal relationship can be drawn. DOSE: not standardized across the studies	16 included studies	Low
Nakase K, Koizumi J, Fukumoto S, Hayashi N, Noguchi N, Nakaminami H. Increased Prevalence of Minocycline-Resistant Staphylococcus epidermidis with tet(M) by Tetracycline Use for Acne Treatment. Microb Drug Resist. 2022 Aug;28(8):861-866. doi: 10.1089/mdr.2021.0319. Epub 2022 Jun 20. PMID: 35723664	179 strains of S epi: Similarly, strains isolated from patients who had used tetracyclines and quinolones showed significantly higher resistance rates to minocycline (hospital, 23.5%; clinics, 39.4%) and levofloxacin (hospital, 81.3%; clinics, 51.4%), respectively, than those of strains isolated from patients who had not used antimicrobials ($p < 0.05$). In contrast, no difference in doxycycline resistance rate was observed between strains isolated from patients who had and had not been on treatment. *the predominance of TetM S epidermitis strains were minocycline resistant but doxycycline sensitive Dose: 100 mg of doxy qday but not validated that patients were taking that.	179 strains 84 patients on tetracyclines but not did not list exact number of people taking doxy Can’t draw conclusions on doxy acne treatment as was lumped together	Low

AMR STIs

Citation	Summary of Findings	Number of Participants	Quality of Evidence
Berçot B, Charreau I, Rousseau C, Delaugerre C, Chidiac C, Pialoux G, Capitant C, Bourgeois-Nicolaos N, Raffi F, Pereyre S, Le Roy C, Senneville E, Meyer L, Bébéar C, Molina JM; ANRS IPERGAY Study Group. High Prevalence and High Rate of Antibiotic Resistance of Mycoplasma genitalium Infections in Men Who Have Sex With Men: A Substudy of the ANRS IPERGAY Pre-exposure Prophylaxis Trial. Clin Infect Dis. 2021 Oct 5;73(7):e2127-e2133. doi: 10.1093/cid/ciaa1832.	200 mg a dose ; max 600 mg a week STI PEP M gen prev in 2 arms were similar over 6 months. They did identify 2 M gen strains with mutations near the TET target site of 16S RNA of undetermined significance.	210 patients on STI PEP were tested for M gen. 32 had M gen.	Low
Bhengraj AR, Vardhan H, Srivastava P, Salhan S, Mittal A. Decreased susceptibility to azithromycin and doxycycline in clinical isolates of Chlamydia trachomatis obtained from recurrently infected female patients in India. Chemotherapy. 2010;56(5):371-7. doi: 10.1159/000314998. Epub 2010 Oct 12.	9 isolates from patients with recurrent Ct. 3 had high MICS to doxy and 2 had been previously treated with doxy (2 out of 3)	163 patients; 51 with Ct; 12 with recurrent Ct yielding 9 isolates	Medium

Military studies on travelers diarrhea

Citation	Summary of Findings	Number of Participants	Quality of Evidence
Arthur JD, Echeverria P, Shanks GD, Karwacki J, Bodhidatta L, Brown JE. A comparative study of gastrointestinal infections in United States soldiers receiving doxycycline or mefloquine for malaria prophylaxis. Am J Trop Med Hyg. 1990 Dec;43(6):608-13. doi: 10.4269/ajtmh.1990.43.608.	People in doxy group were no more likely to have tet-R Campylobacter, ETEC than the mefloquine group. Tet-R non ETEC Ecoli was more common in those on doxy at the end of the training tour (p=0.01) but thought related to location. Military on deployment in Thailand. Doxy vs mefloquine and GI illness. No diff in non-ETEC bacteria resistance. Most of Campy was resistant. No diff in ETEC resistance. Training in Thailand meant participants may have acquired new GI flora that was resistant to Abx NOT taking doxy v mefloquine DOSE: 100 mg doxy qday.	253 soldiers on doxy or mefloquine for malaria prophylaxis for 3 months 12 weeks of doxy 21 Campylobacter isolates 200 non ETEC 34 ETECs	Medium
Buchek G, Mende K, Telu K, Kaiser S, Fraser J, Mitra I, Stam J, Lalani T, Tribble D, Yun HC. Travel-associated multidrug-resistant organism acquisition and risk factors among US military personnel. J Travel Med. 2021 Apr 14;28(3):taab028. doi: 10.1093/jtm/taab028.	Study examined 110 military travelers and 11 took doxy. MDRO collected and examined. No diff in ESBL Enterobacteraciae, no relationship with doxy in the 2-7 isolates.	Small sample size	Low

Military Studies of S aureus

Citation	Summary of Findings	Number of Participants	Quality of Evidence

Citation	Summary of Findings	Number of Participants	Quality of Evidence
Lesens O, Haus-Cheymol R, Dubrous P, Verret C, Spiegel A, Bonnet R, Bes M, Laurichesse H, Beytout J, Etienne J, Migliani R, Koeck JL; Working Group on Cutaneous Infections in the Army. Methicillin-susceptible, doxycycline-resistant Staphylococcus aureus, Côte d'Ivoire. Emerg Infect Dis. 2007 Mar;13(3):488-90. doi: 10.3201/eid1303.060729.	Two outbreaks of doxy-R MSSA skin disease in French soldiers with some on doxy prophy, 100 mg a day. Nasal carriage of PVL + MSSA in soldiers being deployed was associated with a history of doxy use but not doxy-R MSSA. All soldiers with PVL+ doxy R MSSA had been on doxy prophy (n=8) Some impact/ relationship with PVL+ MSSA but sample size is slow.	4 months of doxy	Medium
Mende K, Beckius ML, Zera WC, Yu X, Li P, Tribble DR, Murray CK; Infectious Disease Clinical Research Program Trauma Infectious Disease Outcomes Study Investigative Team. Lack of doxycycline antimalarial prophylaxis impact on Staphylococcus aureus tetracycline resistance. Diagn Microbiol Infect Dis. 2016 Oct;86(2):211-20. doi: 10.1016/j.diagmicrobio.2016.07.014. Epub 2016 Jul 15.	160 patients with a history of military trauma injuries were + for S aureus and isolates were cultured. 23% were tet-R. 25/38 were doxy-R and 68% were from people on antimalarial prophy with doxy. "There was no significant difference regarding methicillin and tetracycline resistance and PFT profiles between the groups of isolates from doxycycline-exposed and unexposed patients. Although the profile of tet genes was not significantly different between the groups, a statistically higher proportion of tet(M) genes were found in doxycycline-exposed patients (p=0.031). Although there was no statistically significant difference related to the overall profile of resistance to other antimicrobials between the two groups, there was a significantly greater proportion of isolates from patients exposed to doxycycline that were resistant to levofloxacin (25% versus 10%; p=0.016), and moxifloxacin (25% versus 10%; p=0.016). In a logistic regression multivariate model, sustaining an injury in Afghanistan was significantly associated with doxycycline exposure (odds ratio: 29.9; 95% Wald confidence interval: 6.3-141.2). Isolate type (e.g., infecting) and occurrence of tet(M) gene were not significantly associated with doxycycline antimalarial prophylaxis."	N= 92 No duration given	Medium

*** Quality of the Evidence Rating**

High = This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

Moderate = This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

Low = This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

Very low = This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

† Substantially different = a large enough difference that it might affect a decision

Last Reviewed: September 21, 2023