**Supplementary file 1.** Overview of the 42 RCTs or quasi-RCTs included in the systematic review and meta-analysis. The underlined antibiotics indicate that resistance measurements were made for this antibiotic, reported and extractable from the studies. Justification for resistance outcome extraction is given in Appendix 3 – table 1.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Type Of Study | Focused pathogen/ Reason for antibiotic treatment | | Objective(S) | Antibiotics used in Study arms | | Explicit Definition Of Resistance Outcome | Secondary Outcomes extracted |
|  |  |  |  | | Less antibiotics | More Antibiotics |  |  |
| Bender et al. (1979) | RCT | Infection prophylaxis for patients with acute leukemia or malignant lymphomas receiving remission induction chemotherapy | Tolerance, suppression of microbial flora, protection against colonisation and infection | | Gentamicin | Gentamicin, and vancomycin | no | All-cause mortality |
| Black et al. (1982) | RCT | enterotoxigenic *Escherichia coli* (ETEC) | Compare two treatments options against ECET. | | Trimethoprim | Trimethoprim, and sulfamethoxazole | no | - |
| Chaisson et al. (1997) | RCT | MAC | Safety and activity | | Clarithromycin, and ethambutol | Clarithromycin, ethambutol, and clofazimine | no | All-cause mortality |
| Cometta et al. (1994) | RCT | Nosocomial pneumonia, nosocomial sepsis, or severe diffuse peritonitis | Clinical efficacy and tolerance, emergence of resistance and risk of superinfection | | Imipenem | Imipenem, and netilmicin | no | Mortality attributable to infection,  treatment failure, treatment failure due to a change of resistance against the study drugs |
| Dawson et al. (2015) | RCT | Mtb | Efficacy, and safety | | Moxifloxacin, pretomanid, and pyrazinamide | Isoniazid, rifampicin, pyrazinamide, and ethambutol | no | Proportion of patients with alterations of the prescribed treatment due to adverse events |
| Dekker et al. (1987) | RCT | Prophylaxis for acute nonlymphocytic or lymphocytic leukemia | Efficacy of protecting against infections | | Ciprofloxacin | Trimethoprim, and sulfamethoxazole | no | All-cause mortality, mortality attributable to infection, acquisition of resistance against non-administered antibiotics |
| (Dickstein et al., 2020) | RCT | Carbapenem resistant, colistin-susceptible, and gram-negative infections | Development of colistin resistance (secondary outcome of a clinical trial) | | Colistin | Colistin, and meropenem | yes | All-cause mortality, proportion of patients with alterations of the prescribed treatment due to adverse events |
| Dubé et al. (1997) | RCT | MAC | Risk of recrudescent MAC bacteraemia, emergence of resistance to clarithromycin. | | Clarithromycin, and clofazimine | Clarithromycin, clofazimine, and ethambutol | no | All-cause mortality, proportion of patients with alterations of the prescribed treatment due to adverse events |
| Durante-Mangoni et al. (2013) | RCT | Extensively drug resistant *Acinetobacter baumannii* | Mortality | | Colistin | Colistin, and rifampicin | yes | All-cause mortality, mortality attributable to infection, treatment failure |
| Fournier et al. (1999) | RCT | MAC | Efficacy and tolerance. | | Clarithromycin, ethambutol | Clarithromycin, ethambutol, and clofazimine | no | All-cause mortality, proportion of patients with alterations of the prescribed treatment due to adverse events |
| Gerecht et al. (1989) | RCT | Cholangitis | Compare a single drug treatment to a two-drug treatment. | | Mezlocillin | Ampicillin, and gentamicin | yes | All-cause mortality, treatment failure as reported in each study, treatment failure due to a change of resistance against the study drugs |
| Gibson et al. (1989) | RCT | Febrile neutropenia | Efficacy and side effects | | Ceftazidime | Azlocillin, and amikacin | no | All-cause mortality, mortality attributable to infection, proportion of patients with alterations of the prescribed treatment due to adverse events, acquisition of resistance against non-administered antibiotics, emergence of resistance against non-administered antibiotics |
| Haase et al. (1984) | RCT | UTI | Efficacy, tolerance, and safety | | Norfloxacin | Trimethoprim, and sulfamethoxazole | no | Treatment failure, acquisition of resistance against non-administered antibiotics |
| Harbarth et al. (2015) | RCT | MRSA | Assess the non-inferiority of a multiple drug treatment in comparison of a single drug treatment. | | Linezolid | Trimethoprim, sulfamethoxazole, and rifampicin | no | All-cause mortality, mortality attributable to infection, treatment failure |
| Hodson et al. (1987) | RCT | Cystic fibrosis patients with *P. aeruginosa* | Compare an oral one drug treatment to an intravenous two drug treatment. | | Ciprofloxacin | Azlocillin, and gentamicin | no | - |
| Hoepelman et al. (1988) | RCT | Serious bacterial infections | Emergence of resistance of fecal flora | | Ceftriaxone | Cefuroxime, and gentamicin | no | Proportion of patients with alterations of the prescribed treatment due to adverse events |
| Hultén et al. (1997) | RCT | *H. pylori* | Antibacterial efficacy, emergence of clarithromycin resistance. | | Clarithromycin | Clarithromycin, and lymecycline | no | - |
| Iravani et al. (1981) | RCT | Acute UTI | Efficacy, treatment effects on fecal flora, resistance emergence in the infecting pathogen | | Nalidixic acid | Trimethoprim, and sulfamethoxazole | no | - |
| Jacobs et al. (1993) | RCT | Bacterial infections in neutropenic children | Efficacy and safety, tolerance, emergence of resistance and risk of superinfection | | Ceftazidime | Ceftazidime, and tobramycin | yes | All-cause mortality, treatment failure, treatment failure due to a change of resistance against the study drugs |
| Jo et al. (2021) | RCT | Determine impact of antibiotics on healthy skin microbiota | Investigate short and long term of the skin microbiome | | Doxcycycline | Trimethoprim, and sulfamethoxazole | no | - |
| Macnab et al. (1994) | Quasi-RCT | Mtb | Efficacy, primary drug resistance, bacteriological conversion rates, compliance, and side effects | | Isoniazid, and rifampicin | Isoniazid, rifampicin, and ethambutol | no | Proportion of patients with alterations of the prescribed treatment due to adverse event |
| Markowitz et al. (1992) | RCT | *S. aureus* | Efficacy and safety | | Vancomycin | Trimethoprim, and sulfamethoxazole | no | All-cause mortality, treatment failure,  proportion of patients with alterations of the prescribed treatment due to adverse events |
| Mavromanolakis et al. (1997) | RCT | Recurrent UTIs | Effect on the aerobic bowel flora, frequency of resistant strains in the fecal flora during and after treatment. | | Norfloxacin, or Nitrofurantoin | Trimethoprim, and sulfamethoxazole | no | - |
| May et al. (1997) | RCT | MAC | Clinical and bacteriological efficacy, safety, tolerability | | Clarithromycin, and clofazimine | Clarithromycin, rifabutin, and ethambutol | no | All-cause mortality, treatment failure, proportion of patients with alterations of the prescribed treatment due to adverse events |
| McCarty et al. (1988) | RCT | Cystic fibrosis patients with *P. aeruginosa* | Safety, pharmacokinetics of a high-dose singe drug treatment, the effectiveness | | Piperacillin | Piperacillin, and tobramycin | no | All-cause mortality, mortality attributable to infection |
| Menon et al. (1986) | RCT | Acute UTI | Efficacy, selection of resistance in Enterobacteriaceae | | Trimethoprim | Trimethoprim, and sulfamethoxazole | no | Acquisition of resistance against non-administered antibiotics |
| Miehlke et al. (1998) | RCT | *H. pylori* | Effectiveness, tolerability | | Amoxicillin | Clarithromycin, and metronidazole | no | Proportion of patients with alterations of the prescribed treatment due to adverse events |
| Parras et al. (1995) | RCT | MRSA | Efficacy to eradicate, safety | | Mupirocin | Sodium fusidate, trimethoprim, and sulfamethoxazole | no | All-cause mortality, proportion of patients with alterations of the prescribed treatment due to adverse events |
| Parry et al. (1977) | Quasi-RCT | *Pulmonary infection* | Effectiveness, treatment failure, treatment success, frequency of ticarcillin resistant organisms, influence of resistance on disease development | | Ticarcillin | Ticarcillin, and gentamicin | no | - |
| Parry et al. (2007) | RCT | Multidrug resistant typhoid fever | Efficacy | | Ofloxacin, or Azithromycin | Ofloxacin, and Azithromycin | no | Treatment failure |
| Paul et al. (2015) | RCT | MRSA | Test whether a two-drug treatment is non-inferior to a two-drug treatment. | | Vancomycin | Trimethoprim, and sulfamethoxazole | yes | All-cause mortality, treatment failure, acquisition of resistance against non-administered antibiotics, emergence of resistance against non-administered antibiotics | |
| Pogue et al. (2021) | RCT | Gram negative resistant bloodstream infections or pneumonia | Assess superiority of a combination of colistin to monotherapy. | | Colistin | Colistin, and meropenem | yes | All-cause mortality, treatment failure |
| Pujol et al. (2021) | RCT | MRSA | Assess treatment success. | | Daptomycin | Daptomycin, and fosfomycin | yes | All-cause mortality, treatment failure, proportion of patients with alterations of the prescribed treatment due to adverse events |
| Rubinstein et al. (1995) | RCT | Gram-negative hospital acquired infections | Efficacy, safety | | Ceftazidime | Ceftriaxone, and Tobramycin | yes | All-cause mortality, mortality attributable to infection, treatment failure, proportion of patients with alterations of the prescribed treatment due to adverse events |
| Schaeffer et al. (1981) | RCT | UTI | Effectiveness, safety, incidence of resistance in faecal and vaginal flora before, and after treatment. | | Cinoxacin | Trimethoprim, and sulfamethoxazole | no | Proportion of patients with alterations of the prescribed treatment due to adverse events |
| Schaeffer and Sisney (1985) | RCT | UTI | Effectiveness, safety, incidence of resistance in fecal and vaginal flora before, and after treatment. | | Norfloxacin | Trimethoprim, and sulfamethoxazole | no | - |
| Smith et al. (1999) | RCT | P. aeruginosa | Efficacy | | Azlocillin | Azlocillin, and tobramycin | no | Acquisition of resistance against non-administered antibiotics, emergence of resistance against non-administered antibiotics |
| Stack et al. (1998) | RCT | *H. pylori* | Efficacy, safety | | Clarithromycin | Clarithromycin, and metronidazole, or amoxycillin | no | - |
| Walsh et al. (1993) | RCT | MRSA | Efficacy of eradication, emergence of resistance, safety | | Novobiocin, and rifampicin | Rifampicin, trimethoprim, and sulfamethoxazole | yes | Treatment failure, acquisition of resistance against non-administered antibiotics, emergence of resistance against non-administered antibiotics |
| Winston et al. (1986) | RCT | Prophylaxis for hematological malignancy patients | Efficacy and safety | | Norfloxacin | Vancomycin, and polymyxin | no | Mortality attributable to infection |
| Winston et al. (1990) | RCT | Prophylaxis for hematological malignancy patients | Efficacy and safety | | Ofloxacin | Vancomycin, and polymyxin | no | - |
| Wurzer et al. (1997) | RCT | *H. pylori* | Effectiveness, emergence of resistance. | | Clarithromycin | Clarithromycin, and amoxycillin | no | - |

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