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Appendix Table. Summary of included studies*

Study, y (reference)	Setting and population	Design	Main interventions	Outcomes	Assessment of evidence
Bradley et al., 1999 (27)	Adult hematology unit in UK, 261 patients who were not carriers of VRE at the start of the study	Prospective ITS with 3 phases of 4, 6, and 5 months. Planned intervention. Case definition: colonization. Other infection control measures consistent through study.	Phase 1: ceftazidime for empiric antimicrobial drug treatment Phase 2: antimicrobial drug policy changed to piperacillin tazobactam. Phase 3: antimicrobial drug policy changed back to ceftazidime.	Microbial: % of patients colonized with VRE fell from 57% in Phase 1 to 19% in Phase 2, then rose again to 36% in Phase 3: significant by log rank test. Drug: significant reduction in ceftazidime use in Phase 2: immediate –227.8 patient days per month, p<0.001; sustained –19.3 patient days per month, p = 0.037.	Statistically significant reduction in risk of colonization with VRE associated with reduction in antimicrobial drug prescribing. No major weaknesses in the study design.
Calil et al., 2001 (28)	Neonatal unit in Brazil, 342 patients in a 30-bed unit (8 intensive care and 22 intermediate care beds)	Prospective ITS with 2 phases of 3 months each. Unplanned intervention. Case definition: colonization. Other infection control measures were introduced during the study and it is not clear how they related to the antimicrobial drug intervention.	Phase 1: usual care. Phase 2: implementation of infection control measures emphasizing hand washing and contact precautions plus an antimicrobial drug policy restricting use of third-generation cephalosporins.	Microbial: cases of multi-resistant *Enterobacter cloacae* colonization per month decreased in Phase 2: immediate –15.51 cases per month (p = 0.054); sustained –2.73 cases per month (p = 0.138). Drug: no reliable data.	Significant reduction in colonization but it is not possible to separate the effects of the infection control measures from the change in antimicrobial drug policy. Several other potentially important weaknesses.
Carling et al., 2003 (17)	Single medium-sized community teaching hospital (affiliated with a University) in US. No obstetric unit or pediatric ICU.	Hybrid retrospective and prospective ITS with 2 phases of 36 and 84 months. Planned intervention. Case definition: infection with CDAD or resistant gram-negative bacteria, MRSA, or VRE. Other infection control measures consistent through study.	Phase 1: automatic 7-day stop order on all antimicrobial drugs, limited reporting of susceptibility tests, and educational program. Phase 2: as Phase 1 plus review of patients receiving target antimicrobial drugs by pharmacist and ID physician, recommendations placed in the case notes.	Microbial: CDAD and resistant *Enterobacteriaceae* in cases per 1,000 admissions. MRSA and VRE as % clinical isolates. Postintervention: there were significant reductions for CDAD: immediate –1.47 cases, p<0.001; sustained –0.81 cases, p = 0.05. Resistant Enterobacteriaceae also reduced: immediate –2.34 cases, p = 0.03; sustained –1.34 cases, p = 0.01. There was no significant change in the % isolates of MRSA or VRE. Drug: authors' regression analysis shows significant reduction in target antimicrobial drugs in Phase 2.	Significant reduction in CDAD cases and resistant Enterobaceriaceae associated with planned antimicrobial drug intervention that resulted in significant changes in antimicrobial drug use. Main weaknesses were the lack of detail about infection control and the case definition for resistant *Enterobacteriaceae.*
Climo, 1998 (18)	Single 703-bed tertiary care hospital in USA	Hybrid retrospective and prospective ITS with 2 phases of 27 and 33 months. Unplanned intervention. Case definition: infection, CDAD. Other infection control measures consistent through study.	Phase 1: infection control only Phase 2: infection control plus restriction of clindamycin.	Microbial: CDAD cases per quarter. The intervention was associated with significant reduction in CDAD cases per quarter: immediate –26.3 cases, p<0.001; sustained –3.8 cases, p<0.001. Drug: no reliable data.	Significant reduction in CDAD cases in phase 2. However, this was an unplanned intervention, there were no reliable data about drug use, and the study had several other potentially important weaknesses.

Study, y (reference)	Setting and population	Design	Main interventions	Outcomes	Assessment of evidence
de Champs et al., 1994 (29)	Single pediatric ICU with 15 ventilator beds and 28 intermediate-care beds in France	Prospective ITS with 2 phases of 7 and 12 months. Unplanned intervention. Case definition: infection by resistant *E cloacae*. Other infection control measures consistent through study.	Phase 1: barrier precautions only. Phase 2: barrier precautions plus removal of gentamicin from the unit and replacement with amikacin.	Microbial: The intervention was associated with significant reduction in resistant *E cloacae* cases per month, immediate –7.47 cases, p<0.001; sustained –1.00 cases, p = 0.002. Drug: no reliable data.	Significant reduction in *E cloacae* cases in phase 2. However, this was an unplanned intervention, there were no reliable data about drug use, and the study had several other potentially important weaknesses.
de Man et al., 2001 (30)	Two similar neonatal ICUs in the same hospital. The study enrolled 436 patients with a mean of 33 weeks gestation.	Prospective cluster controlled clinical trial with crossover with 2 phases of 6 months each. Planned intervention. Case definition: colonization plus clinical isolates. Other infection control measures: consistent through study.	Phase 1: unit A used amoxicillin plus cefotaxime, unit B used penicillin plus tobramycin. Phase 2: antimicrobial drug policies were switched: unit A used penicillin plus tobramycin, unit B used amoxicillin plus cefotaxime.	Microbial: the cefotaxime and amoxicillin regimen was associated with a relative risk of colonization by gram-negative bacteria resistant to cefotaxime or tobramycin of 2.98 (95% CI 1.64–5.38). Drug: cefotaxime plus amoxicillin exposure was 26%–32% of patient days when that regimen was in place *vs.* 1% when penicillin plus tobramycin was used.	Significantly increased risk of colonization associated with the cefotaxime and amoxicillin regimen. However, risk of colonization was also related to length of stay and was significantly shorter in the penicillin plus tobramycin phase.
Gerding et al., 1985 (19)	Single Veterans Administration hospital in US	Prospective ITS with 4 phases of 4, 26, 12, and 12 months. Planned intervention. Case definition: clinical isolates. Other infection control measures not described.	Phase 1: no restriction. Phase 2: gentamicin restricted. Phase 3: amikacin restricted. Phase 4: gentamicin restricted.	Microbial: % of all gram-negative aerobic bacilli resistant to gentamicin. Figure 1 shows resistance to gentamicin varied between 15% and 2% over the study, falling and rising with no clear relationship to changes in antimicrobial drug policy. Drug: no reliable data.	Little evidence that the fluctuations in resistance to gentamicin were related to antimicrobial drug policy changes. Several potentially important design weaknesses.
Khan and Cheesbrough, 2003 (20)	Single 800-bed nonteaching hospital in UK	Prospective ITS with 3 phases of 6, 13, and 5 months. Phase 2 planned, Phase 3 unplanned. Case definition: CDAD infection. Other infection control measures consistent through study.	Phase 1: cefotaxime. Phase 2: ceftriaxone. Phase 3: levofloxacin.	Microbial: Phase 2 was associated with increase in CDAD cases per quarter: immediate +19.7 cases, p = 0.07; sustained +4.7 cases p = 0.07. Phase 3 was associated with sustained reduction in CDAD by –5.8 cases per quarter, p = 0.08. Drug: no reliable data for Phase 1, significant reduction in ceftriaxone use (g per quarter) in Phase 3.	Non significant changes in CDAD were associated with the introduction and restriction of ceftriaxone. Regression to the mean was a plausible alternative explanation for changes in phase 3 and reliable drug data were provided only for phases 2 and 3.
Landman et al., 1990 (21)	Single university hospital in US with 569 discharges per month from medical and surgical services	Retrospective ITS with 2 phases of 29 and 23 months. Planned intervention. Case definition: clinical isolates of resistant bacteria. Other infection control measures: none specific to the bacteria under study.	Phase 1: unrestricted. Phase 2: restriction of third-generation cephalosporins, clindamycin, and vancomycin by requiring approval by an ID physician.	Microbial: intervention was not associated with a significant reduction in the incidence of either ceftazidime-resistant *Klebsiella pneumoniae* or MRSA. However, there was a significant sustained increase in cefotaxime-resistant *Acinetobacter* spp: by +0.337 new cases per 1,000 discharges. Drug: no reliable data.	The intervention was associated with a significant but unintended increase in one of the outcomes and no significant changes in the other. However, there were important weaknesses in the study design.

Study, y (reference)	Setting and population	Design	Main interventions	Outcomes	Assessment of evidence
Lautenbach et al., 2003 (22)	Single 725-bed University hospital in US	Hybrid retrospective and prospective ITS with 2 phases of 36 and 84 months. Unplanned intervention. Case definition: clinical isolates of VRE. Other infection control measures not described.	Phase 1: unrestricted use of antimicrobial drugs. Phase 2: use of vancomycin or third-generation cephalosporins for >72 h required approval by the antimicrobial drug management team. After 24 months any use of vancomycin required approval.	Microbial: regression analysis suggests that the intervention was associated with significant reduction in % VRE but this result was an artifact caused by the first point in the data (1% VRE) and only having 3 preintervention points. Drug: no significant change in vancomycin use (DDD/1,000 patient days)	No evidence supporting control by antimicrobial drug restriction because the restriction did not reduce the use of vancomycin. No data about infection control measures and there were other important weaknesses in the study design.
Leverstein-van Hall et al., 2001 (25)	Neurology and neurosurgery wards in a single 858-bed university hospital in the Netherlands.	Prospective ITS with 2 phases of 1 and 2 months. Unplanned intervention. Case definition: colonization. Other infection control measures consistent through study but only implemented 4 weeks before the start of antimicrobial drug restriction.	Phase 1: stringent barrier precautions. Phase 2: restriction of all antimicrobial drugs by requiring approval by microbiology or ID. Only amikacin or carbapenems used for treatment of gram-negative infection.	Microbial: % prevalence of intestinal colonization by gentamicin-resistant *Enterobacteraiaceae* was decreasing preintervention: by –1.3 % per week and there was no significant change postintervention. Drug: no reliable data.	No evidence supporting control by antimicrobial drug restriction. There were several important weaknesses in the study design.
McNulty et al., 1997 (26)	Care of the elderly unit in a single nonteaching hospital in UK.	Prospective ITS with 2 phases of 7 and 16 months. Unplanned intervention. Case definition: infection, CDAD. Other infection control measures consistent through study.	Phase 1: increased ward cleaning and patient isolation. Phase 2: restriction of cephalosporins by removal from ward stock; infection control measures as in Phase 1.	Microbial: phase 2 was associated with nonsignificant reduction in CDAD: immediate –3.22, cases per month, p = 0.120; sustained –0.50 cases per month, p = 0.230. Drug: intervention was associated with significant reduction in cefuroxime cost: immediate –£501.78 per month, p = 0.015.	Nonsignificant reduction in CDAD cases. This was an unplanned intervention and the study had several other potentially important weaknesses.
Meyer et al., 1993 (23)	A single 487-bed university hospital in US	Hybrid retrospective and prospective ITS with 2 phases of 14 and 11 months. Unplanned intervention. Case definition: infection plus colonization. Other infection control measures: barrier precautions implemented at the same time as ceftazidime restriction.	Phase 1: usual care. Phase 2: barrier precautions for infected or colonized patients plus restriction of ceftazidime. Case notes were reviewed for 133 of the 142 patients with resistant isolates, of whom 52 (39%) met CDC criteria for nosocomial infection.	Microbial: number of cases of ceftazidime-resistant *K. pneumoniae* per 1,000 average daily census. Phase 2 was associated with significant reduction: immediate –38.6 cases, p<0.0001; sustained –6.2 cases, p<0.0001. Drug: drug data are provided for different periods (22 months preintervention and 6 months postintervention) but do show a significant reduction in the number of patients receiving ceftazidime: immediate –26.4 patients, p =0.003; sustained –10.21 patients, p<0.001.	Significant reduction in ceftazidime-resistant *K. pneumoniae* in phase 2 with significant reduction in ceftazidime use. However, it is impossible to separate the effect of ceftazidime restriction from the infection control measures. Regression to the mean was another plausible explanation.
Pear et al., 1994 (24)	A single university hospital in the US with an average daily census of 168 patients	Hybrid retrospective and prospective ITS with 2 phases of 40 and 14 months. Unplanned intervention. Case definition: infection, CDAD. Other infection control measures consistent across study.	Phase 1: hospital staff education, increased use of gloves and improved environmental hygiene. Phase 2: restriction of clindamycin by prior approval by ID physician; infection control measures maintained as in Phase 1.	Microbial: number of CDAD cases per month. Phase 2 was associated with significant reduction, immediate –3.68 cases per month, p = 0.041, sustained –0.32 cases per month, p = 0.134). Drug: no reliable data.	Significant reduction in CDAD in phase 2 but this was an unplanned intervention and there were no reliable data about drug use.

Study, y (reference)	Setting and population	Design	Main interventions	Outcomes	Assessment of evidence
Singh et al., 2000 (31)	Adult surgical and medical ICUs in a single university-affiliated Veterans Administration hospital in US. 81 patients included, mean age 69 years.	Randomized trial with followup of patients until they were discharged from ICU or died. Planned intervention. Case definition: colonization plus clinical isolates. Other infection control measures not described but it is reasonable to assume that they were consistent for the intervention and control patients.	Control group: choice, number, and duration of antimicrobial drugs at the discretion of the care providers. Intervention group: patients received standardized initial therapy (ciprofloxacin IV for 3 days) with assessment at 3 days when antimicrobial drugs were stopped if the patient was judged to be at low risk of pneumonia based on the CPIS score.	Microbial: % patients colonized or infected with resistant bacteria. RR for intervention *vs.* control: 0.36, 95% CI 0.14–0.89. Drug: RR of receiving antimicrobial drugs for > 3 days, intervention *vs.* control: 0.29, 95% CI 0.17–0.48. Clinical: length of ICU stay (9.4 days intervention vs. 14.7 days control; p = 0.04); Nonsignificant reduction in deaths: RR of 30-day death: 0.41, 95% CI 0.16–1.05	Statistically significant reduction in risk of colonization and infection with resistant bacteria associated with reduction in antimicrobial drug prescribing. Clinical noninferiority of the intervention regimen was confirmed. No major weaknesses.
Toltzis et al., 2002 (32)	Single 38-bed neonatal intensive care unit in a University hospital in US. 1,062 episodes of care in infants with mean age 35 weeks	Randomized trial with followup of patients until they were discharged from ICU or died. Planned intervention. Case definition: colonization. Other infection control measures not described but it is reasonable to assume that they were consistent for the intervention and control patients.	Control group: prescribing according to individual preference of physicians. Intervention group: monthly rotation between gentamicin, followed by piperacillin-tazobactam, followed by ceftazidime, followed by gentamicin again.	Microbial: % of patients colonized with resistant bacteria. RR was greater in the Intervention group: 1.40, 95% CI 0.95–2.05. Drug: control patients received predominantly gentamicin. The intervention group received the intended antimicrobial drugs on 84% of all antimicrobial days. No difference in total antimicrobial drug use. Clinical: all cause death was similar: 3.2% intervention vs. 2.3% control.	No evidence supporting control of resistance by antimicrobial drug cycling. No major weaknesses. The authors provide 4 alternative explanations other than failure of cycling: NICU population, rotation too rapid, inclusion of ceftazidime, use of ampicillin in all regimens.

*VRE, vancomycin-resistant enterococci; ITS, interrupted time series; ICU, intensive care unit; CDAD, *Clostridium difficile*–associated diarrhea; MRSA, methicillin-resistant *Staphylococcus aureus*; ID, infectious disease; CI, confidence interval; DDD, defined daily dose; CDC, Centers for Disease Control and Prevention; IV, intravenous; RR, relative risk; CPIS, clinical pulmonary infection score; NICU, neonatal intensive care unit. Additional information is available from www.bsac.org.uk

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