Supplementary data

Appendix 1 – Glossary

AmpC β-lactamases: clinically important cephalosporinases encoded by the chromosomes of many Enterobacteriaceae or (less often) by plasmids. High-level expression confers resistance to penicillins (except temocillin), cephalosporins (except cefepime), aztreonam and penicillin-β-lactamase inhibitor combinations.

Antimicrobial: A substance that kills or inhibits the growth of microorganisms. This includes antibiotics and totally synthetic compounds.

Bacteraemia: The presence of micro-organisms in the blood stream

β-lactamases: Enzymes produced by some bacteria that confer resistance to β-lactam antibiotics such as penicillins and cephalosporins, by breaking down the central structure of the antibiotic.

Carbapenemases: These are β-lactamases that inactivate carbapenems such as meropenem; most also attack and confer resistance to penicillins and cephalosporins

CBA – (Controlled before and after study) is a more limited assessment than interrupted time series because it does not contain an initial pre-study period to examine underlying trends not a post-study period to assess the sustainability of trend, A cross-over study design may exclude bias due to sequential change,

CCG: Clinical Commissioning Group. This is a locality based authority in England responsible for primary care services and placing financial contracts with local hospitals for specific services
CQUIN: NHS England Commissioning for Quality and Innovation payments framework, to encourage care providers to share and continually improve how care is delivered and to achieve transparency and overall improvement in healthcare.

Cluster randomized controlled clinical trial. This is a trial where groups of individuals rather than individuals are randomized to treatment. This complex study design may reduce the chances of one patient’s treatment having an effect on detection of effects in a patient randomized to a different treatment in the same environment.

Colonization: Situation whereby microorganisms establish themselves in a particular environment, such as a body surface, without producing disease.

Community-acquired: infection that is acquired outside of hospitals.

Community-onset or community-associated: usually defined as infection or colonization detected in an outpatient or within 48 hours of hospital admission. Recommended to permit extension to 72 hours.

CCT – (Controlled clinical trial) A clinical trial where there is a comparative arm that is not randomized.

ESBL (extended-spectrum β-lactamase): β-Lactamases that attack cephalosporins with an oxyimino side chain, for example, cefotaxime, ceftriaxone, ceftazidime, ceftolozane as well as the oxyimino-monobactam aztreonam. Unlike AmpC β-lactamases (q.v.) they are inhibited by clavulanic acid and tazobactam and unlike carbapenemases (q.v.) they do not attack carbapenems. Avibactam inhibits them and AmpC β-lactamases.

Healthcare-associated (acquired): infection or colonization detected in an in-patient more than 48 hours after hospital admission or in a resident of a nursing (or residential) home. Recommended to permit extension to 72 hours.
Hospital-onset or Hospital-associated (-acquired): infection or colonization detected in an inpatient more than 48 hours after hospital admission. Recommended to permit extension to 72 hours.

IMP carbapenemase (of MBL class) prevalent particularly in Asia and Australia sometimes in association with a second carbapenemase \( (bla_{KPC}) \) gene

Infection: Invasion by and multiplication of pathogenic microorganisms in the body, producing tissue injury and disease, requiring treatment.

ITS – (Interrupted time series). A series of sequential cases where an intervention is made in the middle of the study as in before and after studies but additional time periods before and after the two comparative periods are included to give information on prior trends and sustainability. studied. There may be further interventions in the series similarly studied.

KPC Klebsiella pneumoniae carbapenemase-producing bacteria are drug-resistant Gram negative bacilli which spread rapidly and cause significant morbidity and mortality. They are the most prevalent carbapenemase producers encoded by the \( bla_{KPC} \) gene, which can be found in other Gram negative species.

MBL (Metallo β-lactamase) producing Gram negative bacteria use a Zn\(^{2+}\) ion in expressing resistance to carbapenems and other B-lactams

MDR GNB – (Multi-drug resistant Gram-negative bacteria) are defined as bacteria resistant to at least three different antibiotic classes or susceptible to only one or two classes.
NDM New Delhi metallo β-lactamase is a carbapenemase located on a mobile genetic element \textit{bla}_{\text{NDM-1}} and is found on plasmids of various sizes. It is found in various species making outbreaks more difficult to identify.

OXA-48 carbapenemases hydrolyze penicillins at a high level but carbapenems at a low level sparing broad spectrum cephalosporins and are no susceptible to β-lactamase inhibitors. Recognition in the laboratory can be difficult. The gene \textit{bla}_{\text{OXA-48}} is carried on a transposon and can be in a plasmid or chromosome.

Outbreak: at least two similar (i.e. not distinct) cases related in time and place

Porins: These are proteins that span the outer membrane of Gram-negative bacteria and mycobacteria forming pores that allow the entry of small water-soluble molecules, including antibiotics.

RCT (randomised controlled trial). Trials where patient allocation to the control and test arms of the study are allocated at random. They can be open label where treating physicians know which arm a patient has been allocated to or blinded where this is not the case. The latter is less likely to be subject to bias.

VIM MBL is a carbapenemase predominantly found in \textit{Pseudomonas aeruginosa} but found in Enterobacteriaceae as well. The genes \textit{bla}_{\text{VIM}} are located on mobile integrons.
Appendix 2 Remit scope and related NICE guidelines

Joint BSAC/HIS/BIA Working Party on Multi-resistant Gram-negative bacteria

2.1. Guideline title

Treatment of MDR Gram-negative bacteria – report from a Joint Working Party

Short title: Treatment of Multi-Drug-Resistant Gram negative bacteria

2.2. Clinical need for the guideline

Epidemiology
There are a rising number of MDR Gram-negative infections across community and hospital care and the dual problems of finding an appropriate antibiotic and preventing spread.
APRHAII has recently produced brief guidelines on infection control and treatment options for these infections.
There is significant interest attracted by the May 2010 BSAC conference examining the dearth of new antibiotics effective against Gram-negative bacteria.
The Department of Health’s recognised that whilst control of MRSA and C difficile has been relatively successful, Gram-negative infections have continued to increase.
Consequent to this is the surveillance subcommittee of APRHAI recommendation that E. coli bacteraemia be included in mandatory surveillance.

Current practice
Members of BSAC and HIS, with the knowledge of the Councils of each, have been discussing the issues surrounding the recent increase in infections with multi-resistant Gram-negative bacteria in UK hospitals.
Following discussions and consideration of the forthcoming APRHAI report we now believe it an appropriate time to set up a Joint Working Party to look at making authoritative recommendations both for treatment and prevention of transmission of these infections.

2.3. The remit

To examine and make recommendations both for treatment and prevention of transmission of multi-drug-resistant (MDR) Gram-negative infections, resulting in the publication of guidelines on:
• current epidemiology and infection control issues; and
• therapeutic issues and antibiotic guidance for treating infections caused by MDR Gram-negative bacteria.

For the purposes of this Working Party, the remit will mainly include infections in critical and non-critical care patients in secondary care. However, the same general principles would apply in community settings, particularly in areas where inappropriate treatment is encouraging selection. Consideration will be given to laboratory testing and susceptibility testing, although only screening and confirmatory tests available in a general microbiology laboratory. The use of antibiotic combinations in the therapy of infections will be considered, both parenteral and oral agents.

2.4. The Guideline

The guideline development process is described on the NICE website and reproduced in Appendix 3. The Working Party will follow the SIGN process when developing guidance including the hosting of a national stakeholder meeting as part of the national stakeholder consultation process.

2.5. The Scope

Defines what the guideline will and will not examine and what the guideline developers will consider. The scope is based on the referral from the three Societies and is the final scope.

2.5.1. Population Groups that will be covered

a) Adults
   Particular consideration given to patients of 65 years and older, and people at high risk of acquiring multi-resistant bacteria such as those requiring care in hospital settings
b) Children over 1 month old

2.5.2. Key clinical issues that will be covered

a) Antimicrobial treatment of MDR Gram-negative infections
b) Antimicrobial stewardship
c) Epidemiology
d) Surveillance

e) Infection prevention: standards, hand and environmental hygiene, organizational structures

*Clinical situations that will not be covered include:*

- Cystic fibrosis
- Community outbreaks

### 2.5.3. Infections that will be covered

Those caused by the following organisms

- *Escherichia coli*, *Klebsiella* spp. including *Klebsiella pneumoniae*, *Enterobacter* spp., *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Proteus* spp., *Serratia* spp., *Citrobacter freundii*, *Morganella morgani*

- Sexually transmitted infections, *Helicobacter* spp. *Salmonella* ssp. and some anaerobes are Gram-negative and are increasingly resistant, but were excluded because relevant public health control actions are substantially different or they have not been researched.

### 2.5.4. Antibiotics that will be considered

*Standard antibiotics currently in use* such as most cephalosporins, coamoxiclav, piperacillin/tazobactam quinolones, temocillin (pivmecillinam is the oral formulation of mecillinam)

*Old antibiotics that have been re-introduced:* such as aminoglycosides (including gentamicin and amikacin), colistin, fosfomycin, nitrofurantoin

*Recently developed antibiotics:* tigecycline, cefepime, new B-lactam-B-lactamase inhibitor combinations and carbapenems or those new agents at preliminary stages of testing.

### 2.5.5. Healthcare settings

All settings in which NHS care is received

### 2.6. Main outcomes

Outputs will be the production of guidelines, which will be approved via a process of national consultation. The intention is to inform and guide practice but also to highlight areas where more research is needed. The following will be produced and published as indicated:
Current epidemiology and infection control issues – Journal of Hospital Infection
Therapeutic issues and antibiotic guidance for treating infections caused by multi-resistant Gram-negatives – Journal of Antimicrobial Chemotherapy
In addition, it is expected that each Journal will carry a leading article or review article on the guidance that is published by the joint societies.

2.7. Recommendations for practice

*Treatment*

*Surveillance*

*Screening*

*Prevention of transmission*

*Cleaning and environment*

2.8. Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. Failure to implement the recommendations would result in greater costs in terms of life expectancy or quality. Screening and isolation will result in significant cost pressures where this is not currently practised, but these costs are set against reduced transmission and fewer cases needing antibiotic treatment. Prolonged isolation can have adverse effects on a patient’s psychological health, so may have additional unexpected costs.

2.9. Patient Representation and Equality

Patient representatives are invited to all meetings and involved in the writing and drafting of the guidelines. As part of these discussions potential impacts on equality of groups sharing protected characteristics are considered and incorporated into the guidelines. Health inequalities associated with socioeconomic factors and with inequities in access for groups to healthcare and social care are considered and opportunities identified to improve health.

2.10. Status

2.10.1 Scope

This is the final scope.
2.10.2 Timing

The development of the guideline recommendation began in July 2011.
Appendix 3 Guideline development process

3.1. Guidance document


3.2. Related NICE guidance


National Institute for Health and Care Excellence. Urinary Tract Infection in Adults. London: NICE; Quality standard [QS90] Published date: June 2015. Available at: https://www.nice.org.uk/guidance/qs90/chapter/introduction


3.3. Process followed

The subject was identified by the Scientific Development Committee of the Healthcare Infection Society in February 2011 and approved by HIS in May 2011. The BSAC Council agreed a similar proposal at the same time. BIA Council agreed to join in September 2011. The members were chosen to reflect the range of stakeholders and not limited to members of the three Societies. The questions were decided at the first meeting of the
Group in November 2011 from issues presented to the members and patient representatives by staff and patients in the preceding months. Each was debated by the Group before adoption. Enhance Reviews was paid for the search and data extraction. Working Party members were not paid except for travel expenses.

3.4. Conflict of Interests
Conflicts of interest were registered at the outset and renewed during the process. They are stated in the Transparency declaration of the Report. In the event of a potential conflict being identified, the Working Party agreed that the member should not contribute to the section affected. With one exception, no interests were declared that required any actions and this related to the infection control paper produced by the working party.

3.5. PICO
Patients: All patient groups were included. The guideline is careful not to make recommendations which may prejudice clinical care based on gender, age, ethnicity or socio-economic status.

Interventions: interventions were identified in the literature to generate intervention specific recommendations

Comparisons: comparisons between intervention and standard management were used;

Outcomes were objective referring to length of hospital stay, mortality, rate of acquisition or infection.

3.6. Systematic Review Questions: Infection Control
1. What is the definition of Multidrug Resistant Gram-negative bacilli?
2. What Gram-negative bacilli cause infection control problems?
3. What are the relative contributions of community and hospital acquisition?
4. What is the evidence for reservoir and spread of multiresistant Gram-negatives in Care Homes and secondary care?
5. What is the role of agricultural use of sewage and antibiotic treatment in veterinary practice in spreading ESBL?
6. What insights has national E. coli bacteraemia surveillance provided?
7. What is the role for screening in patients and staff?
8. What organisms should screening include?
9. Who, how and when to screen patients for Multidrug Resistant Gram-negative bacilli?
10. What can be done concerning patients unable to consent to a rectal swab?
11. How frequently does screening need to be performed?
12. Is there evidence for effective interventions on positive patients i.e. can carriage be cleared?
13. Selective decontamination: Why is it not used? Is there a role?
14. When should the environment be sampled?
15. What is the evidence that respiratory equipment contributes to transmission?
16. What national surveillance is performed and how should it be developed?
17. What is the evidence that sensor taps contribute to transmission?
18. Is there any cleaning method more effective than others at removing the Multidrug Resistant Gram-negative bacilli from the environment?
19. What is the evidence that infection control precautions prevent transmission?
20. Are standard infection control measures sufficient to stop transmission?
21. What are the minimum standards to stop spread in public areas, primary care or care homes?
22. Is there evidence for high/low risk areas within a healthcare facility?
23. Are there any organisational structures within a healthcare facility that play a role in the successful control of multi-resistant Gram-negative bacilli?
24. How should we undertake local screening, why is it important and how should it be interpreted?
25. At what point should passive surveillance switch to active surveillance i.e. screening?
26. What is the role of isolation in the care home/hospital settings?
Is there evidence of differences between organisms in respect of transmission, morbidity and mortality:

3.7. Antimicrobial Chemotherapy - Systematic Review Questions

1. What is the clinical importance of carbapenemases versus AmpC and CTX-M strains?
2. What impact have returning travellers made on UK epidemiology?
3. What is the global epidemiology of MDR-GNR?
4. How do Multidrug Resistant Enterobacteriaceae differ from the non-fermenters in terms of their prevalence and associated resistance genes?
5. What is the efficacy of carbapenems, mecillinam, temocillin, fosfomycin and colistin against specific pathogens?
6. What are the recommended antibiotics for community/secondary/tertiary care?
7. What is the threshold level of resistance for changing choice of empirical treatment for urinary infection?
Appendix 4 Systematic Review

4.1. Databases and Search terms Used 23/5/14

4.1.1. Databases

The Cochrane Library; MEDLINE; EMBASE; CINAHL

MeSH Terms See 4.2.

Free text terms. See 4.2.

Search Date: Medline 1946-2014; Embase 1980-2012; CINAHL (1984-2012)

Search Results (Figure 1)

Total number of articles located after duplicates removed = 2523

Sift 1 Criteria

Abstract screening: Systematic review, primary research, infection relates to MDR Gram-negative infection, informs one or more review question

Articles Retrieved

Total number of studies selected = 597

Sift 2 Criteria

Full text confirms that the article is primary research (randomised controlled trial, non-randomised controlled trials, controlled before and after studies, interrupted time series, case control study, case series, prospective cohort, systematic review; informs one or more of the review questions.

Articles selected for appraisal (10 full text publications could not be retrieved)

Total number of studies selected = 49

Critical appraisal

Articles presenting primary research or a systematic review and meeting the sift criteria were critically appraised by two reviewers using SIGN and EPOC criteria. Consensus was achieved through discussion

Accepted and Rejected Evidence

No meta analyses were available

Accepted after critical appraisal 49

Rejected after critical appraisal 0
### 4.2. Search

#### 4.2.1. CINAHL (January 1984-December 2012)

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<td>S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46</td>
<td>16,726</td>
</tr>
<tr>
<td>#</td>
<td>Query</td>
<td>Results</td>
</tr>
<tr>
<td>----</td>
<td>----------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>S46</td>
<td>TI ( (belcomycin or colicort or colimycin* or colisitin or colisticin or Colistin or colistine or colomycin or (coly n1 mycin) or colymicin or colymycin or coly-mycin or colymycin or (Polymyxin n1 E) or totazina) ) OR AB ( (belcomycin or colicort or colimycin* or colisitin or colisticin or Colistin or colistine or colomycin or (coly n1 mycin) or colymicin or colymycin or coly-mycin or colymycin or (Polymyxin n1 E) or totazina) )</td>
<td>171</td>
</tr>
<tr>
<td>S45</td>
<td>(MH 'Colistin')</td>
<td>134</td>
</tr>
<tr>
<td>S44</td>
<td>TI ( ((amdinocillin n1 pivoxil) or (FL n1 '1039') or FL1039 or fl1039 or FL-1039 or pivaminocillin or Pivmecillinam or Selexid or coactabs or (ro n1 '109071') or (ro10 n1 '9071') or ro109071) ) OR AB ( ((amdinocillin n1 pivoxil) or (FL n1 '1039') or FL1039 or fl1039 or FL-1039 or pivaminocillin or Pivmecillinam or Selexid or coactabs or (ro n1 '109071') or (ro10 n1 '9071') or ro109071) )</td>
<td>13</td>
</tr>
<tr>
<td>S43</td>
<td>TI ( ((Cephalosporanic n1 Acid*) or Cephalosporin* or Cefamandole or Cefoperazone or Cefazolin or Cefonicid or Cefsulodin or Cephacetrile or Cefotaxime or Cephalothin or Cephapirin or Cephaalexin or Cefaclor or Cefadroxil or Cephaloglycin or Cephradine or Cephaloridine or Ceftazidime or Cephamycins or Cefmetazole or Cefotetan or Cefoxitin) ) OR AB ( ((Cephalosporanic n1 Acid*) or Cephalosporin* or Cefamandole or Cefoperazone or Cefazolin or Cefonicid or Cefsulodin or Cephacetrile or Cefotaxime or Cephalothin or Cephapirin or Cephaalexin or Cefaclor or Cefadroxil or Cephaloglycin or Cephradine or Cephaloridine or Ceftazidime or Cephamycins or Cefmetazole or Cefotetan or Cefoxitin) )</td>
<td>1,569</td>
</tr>
<tr>
<td>S42</td>
<td>TI ( (Axepim* or bmy 28142 or bmy28142 or BMY-28142 or Cefepim* or cefepitax or ceficad or cepimax or forzyn beta or maxcef or maxfro or maxipime or Quadrocef) ) OR AB ( (Axepim* or bmy 28142 or bmy28142 or BMY-28142 or Cefepim* or cefepitax or ceficad or cepimax or forzyn beta or maxcef or maxfro or maxipime or Quadrocef) )</td>
<td>171</td>
</tr>
<tr>
<td>S41</td>
<td>(MH 'Cephalosporins+')</td>
<td>2,105</td>
</tr>
<tr>
<td>#</td>
<td>Query</td>
<td>Results</td>
</tr>
<tr>
<td>----</td>
<td>----------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>S40</td>
<td>TI ( (berkfurin or biofurin or chemiofuran or dantafur or f 30 or f30 or fua-med or furaben or furadantin* or furadantoin or furadina or furadoine or furadonin or furadonine or furalan or furanpur or furantocompren or furantoin* or furobactina or furofen or furophen or furin or ituran or ivadantin or macrobid or macrodantin* or macrofurin or macrofuradantin* or nitrofurin or nitrofuradantoin* or nitrofurantoin* or nitrofurantione or nitrofurantoin* or nitrofurin or novofuran or nsc 2107 or nsc2107 or orafuran or parfuran or phenurin or (potassium n1 furagin) or ralodantin or trocurine or urantin or (uro n1 tablinen) or urodil or urodin or urofuran or urolong or urotablelinen or urotablinen or urotoina or uvamin ) ) OR AB ( (berkfurin or biofurin or chemiofuran or dantafur or f 30 or f30 or fua-med or furaben or furadantin* or furadantoin or furadina or furadoine or furadonin or furadonine or furalan or furanpur or furantocompren or furantoin* or furobactina or furofen or furophen or furin or ituran or ivadantin or macrobid or macrodantin* or macrofurin or macrofuradantin* or nitrofurin or nitrofuradantoin* or nitrofurantoin* or nitrofurantione or nitrofurantoin* or nitrofurin or novofuran or nsc 2107 or nsc2107 or orafuran or parfuran or phenurin or (potassium n1 furagin) or ralodantin or trocurine or urantin or (uro n1 tablinen) or urodil or urodin or urofuran or urolong or urotablelinen or urotablinen or urotoina or uvamin ) )</td>
<td>325</td>
</tr>
<tr>
<td>S39</td>
<td>TI ( (((az n1 threonam) or azactam or azenam or azthreonam or aztreonam or (corus n1 ‘1020’)) or dynabiotic or primbactam or SQ 26,776 or sq 26,776 or sq 26776 or sq 26776 or sq 26276 or sq26776 or sq 26776 or urobactam ) ) OR AB ( (((az n1 threonam) or azactam or azenam or azthreonam or aztreonam or (corus n1 ‘1020’)) or dynabiotic or primbactam or SQ 26,776 or sq 26,776 or sq 26776 or sq 26776 or sq 26276 or sq26776 or sq 26776 or urobactam ) )</td>
<td>96</td>
</tr>
<tr>
<td>S38</td>
<td>(MH ‘Aztreonam’)</td>
<td>54</td>
</tr>
<tr>
<td>S37</td>
<td>TI ( (fosfocil or fosfocin or fosfocina or fosfomicin or fosfomycin or fosfonomycin or ‘mk 0955’ or mk 955 or mk0955 or mk955 or monuril or phosphomycin or phosphonomycin) ) OR AB ( (fosfocil or fosfocin or fosfocina or fosfomicin or fosfomycin or fosfonomycin or ‘mk 0955’ or mk 955 or mk0955 or mk955 or monuril or phosphomycin or phosphonomycin) )</td>
<td>57</td>
</tr>
<tr>
<td>#</td>
<td>Query</td>
<td>Results</td>
</tr>
<tr>
<td>----</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>S36</td>
<td>TI ( (akacin or akicin or amicacina or amicasil or amicin or amiglymide v or amikacin* or amikafur or amikalem or amikan or amikayect or amikin or amiklin or amikozit or amiktam or amitracin or amixin or amukin or apalin or bb k 8 or bb k8 or bbk 8 or bb-k 8 or bbk8 or bbk-8 or bb-k8 or biclin or biklin or biokacin or briclin or briklin or chemacin or cinmik or fabianol or gamikal or glukamin or kacinth-a or kanbine or kormakin or likacin or lukadin or miacin or mikasome or onikin or oprad or orlobin or pediakin or pierami or riklinak or savox or selaxa or selemycin or sulfate amikacin or tybikin or vs 107 or vs107 or yectamid) ) OR AB ( (akacin or akicin or amicacina or amicasil or amicin or amiglymide v or amikacin* or amikafur or amikalem or amikan or amikayect or amikin or amiklin or amikozit or amiktam or amitracin or amixin or amukin or apalin or bb k 8 or bb k8 or bbk 8 or bb-k 8 or bbk8 or bbk-8 or bb-k8 or biclin or biklin or biokacin or briclin or briklin or chemacin or cinmik or fabianol or gamikal or glukamin or kacinth-a or kanbine or kormakin or likacin or lukadin or miacin or mikasome or onikin or oprad or orlobin or pediakin or pierami or riklinak or savox or selaxa or selemycin or sulfate amikacin or tybikin or vs 107 or vs107 or yectamid) )</td>
<td>342</td>
</tr>
<tr>
<td>S35</td>
<td>(MH 'Amikacin')</td>
<td>140</td>
</tr>
<tr>
<td>#</td>
<td>Query</td>
<td>Results</td>
</tr>
<tr>
<td>----</td>
<td>----------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>S34</td>
<td><strong>TI</strong> ( (adelanin or alcomicin or apigent or apogen or apoten or azupel or bactiderm or biogaracin or cidomycin or danigen or dermogen or dianfarma or dispagent or duragentam* or epigent or (frieso n1 gent) or garabiotic or garalone or garamicin* or garamycin or garbilocin or gencin or gendril or genoptic or genrex or gensumycin or gentabiotic or gentabiox or gentac or gentacidin or gentacin or gentacor or gentacycol or gentacyl or gentafair or gentagram or gentak or gental or gentaline or gentalline or gentalol or gentalyx or gentamax or gentame* or gentamin or gentamycin* or gentamyl or gentamytrex or gentaplus or gentarad or gentasil or gentasol or gentasone or gentasporin or gentatrim or gentavet or genticin* or genticyn or gentiderm or gentimycin or gentocin or gentogram or gentomycin or genum or geomyecine or gevramycin or g-mycin or gmytin or g-mythicin or grammicin or hexamycin or jenamicin or konigen or lacromycin or lisagent or martigena or migenta or miragentina or miramycin or nichogencin or nsc 82261 or nsc82261 or obogen or ocugenta or ocu-mycin or oftagen or optagram or optagen or optigen or opt-genta or ottogenate or pyogenta or refobacin or ribomicin or rigaminol or rocy gen or rovixida or rupegen or sagestam or sch 9724 or sch9724 or sedanazin or servigenta or skinfect or sulmycin or tangyn or u-gencin or versigen or yectamicina) ) OR AB ( (adelanin or alcomicin or apigent or apogen or apoten or azupel or bactiderm or biogaracin or bristagen or cidomycin or danigen or dermogen or dianfarma or dispagent or duragentam* or epigent or (frieso n1 gent) or garabiotic or garalone or garamicin* or garamycin or garbilocin or gencin or gendril or genoptic or genrex or gensumycin or gentabiotic or gentabiox or gentac or gentacidin or gentacin or gentacor or gentacycol or gentacyl or gentafair or gentagram or gentak or gental or gentaline or gentalline or gentalol or gentalyx or gentamax or gentame* or gentamin or gentamycin* or gentamyl or gentamytrex or gentaplus or gentarad or gentasil or gentasol or gentasone or gentasporin or gentatrim or gentavet or genticin* or genticyn or gentiderm or gentimycin or gentocin or gentogram or gentomycin or genum or geomyecine or gevramycin or g-mycin or gmytin or g-mythicin or grammicin or hexamycin or jenamicin or konigen or lacromycin or lisagent or martigena or migenta or miragentina or miramycin or nichogencin or nsc 82261 or nsc82261 or obogen or ocugenta or ocu-mycin or oftagen or optagram or optagen or optigen or opt-genta or ottogenate or pyogenta or refobacin or ribomicin or rigaminol or rocy gen or rovixida or rupegen or sagestam or sch 9724 or sch9724 or sedanazin or servigenta or skinfect or sulmycin or tangyn or u-gencin or versigen or yectamicina) )</td>
<td>993</td>
</tr>
<tr>
<td>S33</td>
<td><strong>MH ‘Gentamicins’</strong></td>
<td>808</td>
</tr>
<tr>
<td>#</td>
<td>Query</td>
<td>Results</td>
</tr>
<tr>
<td>----</td>
<td>----------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>S32</td>
<td>TI ( (Aminoglycosides or Anthracyclines or Aclarubicin or Daunorubicin or Plicamycin or Butirosin Sulfate or Sisomicin or Hygromycin B or Kanamycin or Dibekacin or Nebramycin or Metrizamide or Neomycin or Framycetin or Paromomycin or Ribostamycin or Puromycin or Spectinomycin or Streptomycin or Dihydrostreptomycin Sulfate or Streptothricins or Streptozocin) ) OR AB ( (Aminoglycosides or Anthracyclines or Aclarubicin or Daunorubicin or Plicamycin or Butirosin Sulfate or Sisomicin or Hygromycin B or Kanamycin or Dibekacin or Nebramycin or Metrizamide or Neomycin or Framycetin or Paromomycin or Ribostamycin or Puromycin or Spectinomycin or Streptomycin or Dihydrostreptomycin Sulfate or Streptothricins or Streptozocin) )</td>
<td>1,269</td>
</tr>
<tr>
<td>S31</td>
<td>(MH ‘Aminoglycosides+’)</td>
<td>6,215</td>
</tr>
<tr>
<td>S30</td>
<td>TI ( ((chinolone n1 derivative) or fluoroquinolones or (haloquinolone n1 derivative) or ketoquinolines or oxoquinolines or quinolinones or quinolones) ) OR AB ( ((chinolone n1 derivative) or fluoroquinolones or (haloquinolone n1 derivative) or ketoquinolines or oxoquinolines or quinolinones or quinolones) )</td>
<td>834</td>
</tr>
<tr>
<td>S29</td>
<td>(MH ‘Quinolines+’) OR (MH ‘Antiinfective Agents, Quinolone+’)</td>
<td>4,842</td>
</tr>
<tr>
<td>S28</td>
<td>TI ( (tigecycline or (tbg n1 mino) or tygacil or gar 936 or gar936 or (tert n1 butylglycinamido*)) ) OR AB ( (tigecycline or (tbg n1 mino) or tygacil or gar 936 or gar936 or (tert n1 butylglycinamido*)) )</td>
<td>208</td>
</tr>
<tr>
<td>S27</td>
<td>TI ( ((brl n1 ‘17421’) or brl17421 or (thiophenemalonamic n1 acid) or negaban or temocillin or temopen) ) OR AB ( ((brl n1 ‘17421’) or brl17421 or (thiophenemalonamic n1 acid) or negaban or temocillin or temopen) )</td>
<td>1</td>
</tr>
<tr>
<td>#</td>
<td>Query</td>
<td>Results</td>
</tr>
<tr>
<td>----</td>
<td>----------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>S26</td>
<td>TI ((aclam or aktil or ambilan or amoca or amoclan or amoclav or amoksiklav or amolanic or amometin or (amox n1 clav) or amox-clav or (amoxi n1 plus) or (amoxNear/3clavulan*) or amoxiclav or amoxiclav-bid or amoxiclav-teva or amoxskilav or amoxsllin or (amoxycillin-clavulanic n1 acid) or ancla or (auclatin n1 duo) or augamox or augmaxcil or augmentan or augmentin* or augmex or augpen or (augucillin n1 duo) or augurcin or ausclav or auspilic or bactiv or bactoclav or bioclavid or (brl n1 '25000') or brl25000 or brl-25000 or cavumox or ciblor or (clacinill n1 duo) or clamax or clamentin or clamobit or clamonex or clamovid or clamoxin or (clamoxyl n1 duo*) or clarin-duo or clavamox or clavar or clavinex or clavodar or clavoxil or (clavoxilin n1 plus) or clavubactin or clavudale or clavulanate-amoxicilin or clavulin or (clavulox n1 duo) or clavumox or (co n1 amoxiclav) or (co n1 amoxyclav) or coamoxiclav or co-amoxiclav or coamoxyclav or (cramon n1 duo) or (croanan n1 duo) or curam or danoclav or (darzitil n1 plus) or e-moxclav or enhancin or Fleming or fleming or fugentin or (fullicilina n1 plus) or gumentin or hibiotic or incilav or klamanex or kmoxlilin or lactamox or lansiclav or moxiclav or moxicile or moxyclav or natravox or nufaclav or palentin or quali-mentin or ranclav or spektramox or stacillin or suplentin or synermox or synulox or (velamox n1 cl) or vestaclav or viaclav or vulamox or xiclavl or (zami n1 '8503')) ) OR AB ((aclam or aktil or ambilan or amoca or amoclan or amoclav or amoclav or amoksiklav or amolanic or amometin or (amox n1 clav) or amox-clav or (amoxi n1 plus) or (amoxNear/3clavulan*) or amoxiclav or amoxiclav-bid or amoxiclav-teva or amoxskilav or amoxsllin or (amoxycillin-clavulanic n1 acid) or ancla or (auclatin n1 duo) or augamox or augmaxcil or augmentan or augmentin* or augmex or augpen or (augucillin n1 duo) or augurcin or ausclav or auspilic or bactiv or bactoclav or bioclavid or (brl n1 '25000') or brl25000 or brl-25000 or cavumox or ciblor or (clacinill n1 duo) or clamax or clamentin or clamobit or clamonex or clamovid or clamoxin or (clamoxyl n1 duo*) or clarin-duo or clavamox or clavar or clavinex or clavodar or clavoxil or (clavoxilin n1 plus) or clavubactin or clavudale or clavulanate-amoxicilin or clavulin or (clavulox n1 duo) or clavumox or (co n1 amoxiclav) or (co n1 amoxyclav) or coamoxiclav or co-amoxiclav or coamoxyclav or (cramon n1 duo) or (croanan n1 duo) or curam or danoclav or (darzitil n1 plus) or e-moxclav or enhancin or Fleming or fugentin or (fullicilina n1 plus) or gumentin or hibiotic or incilav or klamanex or kmoxlilin or lactamox or lansiclav or moxiclav or moxicile or moxyclav or natravox or nufaclav or palentin or quali-mentin or ranclav or spektramox or stacillin or suplentin or synermox or synulox or (velamox n1 cl) or vestaclav or viaclav or vulamox or xiclavl or (zami n1 '8503')) )</td>
<td>805</td>
</tr>
<tr>
<td>#</td>
<td>Query</td>
<td>Results</td>
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<tr>
<td>-----</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>S25</td>
<td>TI ( (cl 307579 or cl298741 or cl307579 or tazabactam or tazobac* or tazocel or tazocillin* or tazocin or tazomax or tazonam or tazopril or yp 14 or yp14 or ytr 830 or ytr 830h or ytr830 or ytr830h or zosyn ) ) OR AB ( (cl 307579 or cl298741 or cl307579 or tazabactam or tazobac* or tazocel or tazocillin* or tazocin or tazomax or tazonam or tazopril or yp 14 or yp14 or ytr 830 or ytr 830h or ytr830 or ytr830h or zosyn ) )</td>
<td>247</td>
</tr>
<tr>
<td>S24</td>
<td>TI ( (acopex or avocin or cl 227,193 or Cl 227193 or cl 227193 or cl 227,193 or cl227193 or cl-227193 or cl-227,193 or cypercil or hishiyaclorin or ivacin or penticillin or penticillin or picrocin or picillin* or pipril or pipra-hameln or pipercillin or piperilline or pipraci* or pipraks or pipril or piprilin or pitamycin or t 1220 or t1220 or t-1220 or taiperacillin ) ) OR AB ( (acopex or avocin or cl 227,193 or Cl 227193 or cl 227193 or cl 227,193 or cl227193 or cl-227193 or cl-227,193 or cypercil or hishiyaclorin or ivacin or penticillin or penticillin or picrocin or picillin* or pipril or pipra-hameln or pipercillin or piperilline or pipraci* or pipraks or pipril or piprilin or pitamycin or t 1220 or t1220 or t-1220 or taiperacillin ) )</td>
<td>296</td>
</tr>
<tr>
<td>S23</td>
<td>TI ( (Carbapenem* or doripenem or ertapenem or Imipemide or Imipenem or Invanoz or Invanz or meropenem or Merrem or ‘MK 0787’ or MK0787 or MK-0787 or N Formimidoylthienamycin or N-Formimidoylthienamycin or Penem or Ronem or S 4661 or S-4661 or SM 7338 or SM-7338 or Thienamycin*) ) OR AB ( (Carbapenem* or doripenem or ertapenem or Imipemide or Imipenem or Invanoz or Invanz or meropenem or Merrem or ‘MK 0787’ or MK0787 or MK-0787 or N Formimidoylthienamycin or N-Formimidoylthienamycin or Penem or Ronem or S 4661 or S-4661 or SM 7338 or SM-7338 or Thienamycin*) )</td>
<td>974</td>
</tr>
<tr>
<td>S22</td>
<td>(MH ‘Carbapenems+’)</td>
<td>559</td>
</tr>
<tr>
<td>S21</td>
<td>S19 OR S20</td>
<td>14,473</td>
</tr>
<tr>
<td>S20</td>
<td>(MH ‘Drug Resistance, Microbial+)</td>
<td>14,182</td>
</tr>
<tr>
<td>S19</td>
<td>TI ( (multiresistant or (multi n1 resistan*)) ) OR AB ( (multiresistant or (multi n1 resistan*)) )</td>
<td>604</td>
</tr>
<tr>
<td>S18</td>
<td>S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17</td>
<td>7,706</td>
</tr>
<tr>
<td>#</td>
<td>Query</td>
<td>Results</td>
</tr>
<tr>
<td>----</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>S17</td>
<td><strong>TI</strong> ( ((bacillus n1 morgan*) or (bacterium n1 morgana) or (morganella n1 morgagni*) or (morganella n1 morganii) or (proteus n1 morgagni) or (proteus n1 morgana*) or (morganella n1 morgagni) or (proteus n1 morgagni) or (proteus n1 morgana) ) OR <strong>AB</strong> ( ((bacillus n1 morgan*) or (bacterium n1 morgana) or (morganella n1 morgagni*) or (morganella n1 morganii) or (proteus n1 morgagni) or (proteus n1 morgana*) or (morganella n1 morgagni) or (proteus n1 morgagni) or (proteus n1 morgana) ) )</td>
<td>20</td>
</tr>
<tr>
<td>S16</td>
<td><strong>TI</strong> ( ((Citrobacter n1 freundii) or (bacterium n1 freundii) or (Escherichia n1 freundii)) ) OR <strong>AB</strong> ( ((Citrobacter n1 freundii) or (bacterium n1 freundii) or (Escherichia n1 freundii)) )</td>
<td>32</td>
</tr>
<tr>
<td>S15</td>
<td>(MH ‘Citrobacter’)</td>
<td>40</td>
</tr>
<tr>
<td>S14</td>
<td><strong>TI</strong> Serratia OR <strong>AB</strong> Serratia</td>
<td>238</td>
</tr>
<tr>
<td>S13</td>
<td>(MH ‘Serratia’) OR (MH ‘Serratia Infections’)</td>
<td>174</td>
</tr>
<tr>
<td>S12</td>
<td><strong>TI</strong> Proteus OR <strong>AB</strong> Proteus</td>
<td>257</td>
</tr>
<tr>
<td>S11</td>
<td>(MH ‘Proteus’) OR (MH ‘Proteus Infections’)</td>
<td>118</td>
</tr>
<tr>
<td>S10</td>
<td><strong>TI</strong> ( (Acinetobacter or mima or mimae or herellea or acinetobacterium) ) OR <strong>AB</strong> ( (Acinetobacter or mima or mimae or herellea or acinetobacterium) )</td>
<td>889</td>
</tr>
<tr>
<td>S9</td>
<td>(MH ‘Acinetobacter Infections’)</td>
<td>581</td>
</tr>
<tr>
<td>S8</td>
<td><strong>TI</strong> ‘p. aeruginosa’ OR <strong>AB</strong> ‘p. aeruginosa’</td>
<td>610</td>
</tr>
<tr>
<td>S7</td>
<td><strong>TI</strong> ( ((bacillus n1 pyocyaneus) or (bacterium n1 (aeruginosum or pyocyaneum)) or (blue n1 apus) or (Pseudomonas n1 (aeruginosa or aureofaciens or pyoceanus or pyocyanea or pyocyanea))) ) OR <strong>AB</strong> ( ((bacillus n1 pyocyaneus) or (bacterium n1 (aeruginosum or pyocyaneum)) or (blue n1 apus) or (Pseudomonas n1 (aeruginosa or aureofaciens or pyoceanus or pyocyanea or pyocyanea))) )</td>
<td>1,855</td>
</tr>
<tr>
<td>S6</td>
<td><strong>TI</strong> ( (enterobacter or aerobacter) ) OR <strong>AB</strong> ( (enterobacter or aerobacter) )</td>
<td>370</td>
</tr>
<tr>
<td>S5</td>
<td><strong>TI</strong> ( ‘k. pneumoniae’ or ‘b. friedlander’) ) OR <strong>AB</strong> ( (‘k. pneumoniae’ or ‘b. friedlander’) )</td>
<td>200</td>
</tr>
<tr>
<td>#</td>
<td>Query</td>
<td>Results</td>
</tr>
<tr>
<td>----</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>S4</td>
<td>TI ( (klebsiella or Calymmatobacterium or (aerobacter n1 aerogenes) or ((bacillus or bacterium) n1 pneumonia) or (fiedlaender or Friedlander) n1 bacillus) or (Hyalococcus n1 pneumonia) or Pneumobacillus ) OR AB ( (klebsiella or Calymmatobacterium or (aerobacter n1 aerogenes) or ((bacillus or bacterium) n1 pneumonia) or (fiedlaender or Friedlander) n1 bacillus) or (Hyalococcus n1 pneumonia) or Pneumobacillus ) )</td>
<td>1,039</td>
</tr>
<tr>
<td>S3</td>
<td>(MH ‘Klebsiella’) OR (MH ‘Klebsiella Infections’)</td>
<td>835</td>
</tr>
<tr>
<td>S2</td>
<td>TI ( (Eaggec or (escherichia n1 coli) or (e n1 coli) or (alkalescens-dispar n1 group) or (bacillus n1 escherichii) or (Coli n1 bacillus) or (Coli n1 bacterium) or colibacillus or (colon n1 bacillus)) ) OR AB ( (Eaggec or (escherichia n1 coli) or (e n1 coli) or (alkalescens-dispar n1 group) or (bacillus n1 escherichii) or (Coli n1 bacillus) or (Coli n1 bacterium) or colibacillus or (colon n1 bacillus)) )</td>
<td>2,914</td>
</tr>
<tr>
<td>S1</td>
<td>(MH ‘Escherichia Coli’) OR (MH ‘Escherichia Coli Infections’)</td>
<td>2,983</td>
</tr>
</tbody>
</table>

**4.2.2. Cochrane Library (Issue 11, 2012)**

ID Search

#1 MeSH descriptor: [Escherichia coli] explode all trees

#2 (Eaggec or (escherichia near/1 coli) or (e near/1 coli) or (alkalescens-dispar near/1 group) or (bacillus near/1 escherichii) or (Coli near/1 bacillus) or (Coli near/1 bacterium) or colibacillus or (colon near/1 bacillus)):ti,ab,kw (Word variations have been searched)

#3 MeSH descriptor: [Klebsiella] explode all trees

#4 (klebsiella or Calymmatobacterium or (aerobacter near/1 aerogenes) or ((bacillus or bacterium) near/1 pneumonia) or (fiedlaender or Friedlander) near/1 bacillus) or (Hyalococcus near/1 pneumonia) or Pneumobacillus):ti,ab,kw (Word variations have been searched)

#5 k. pneumoniae or b. friedlander:ti,ab,kw (Word variations have been searched)

#6 MeSH descriptor: [Enterobacter] explode all trees

#7 (enterobacter or aerobacter):ti,ab,kw (Word variations have been searched)

#8 MeSH descriptor: [Pseudomonas aeruginosa] explode all trees

#9 ((bacillus near/1 pyocyaneus) or (bacterium near/1 (aeruginosum or pyocyaneum)) or (blue near/1 apus) or (Pseudomonas near/1 (aeruginosa or aureofaciens or pyoceaneus or pyocyanea or pyocyanus))):ti,ab,kw (Word variations have been searched)

#10 p. aeruginosa:ti,ab,kw (Word variations have been searched)

#11 MeSH descriptor: [Acinetobacter] explode all trees
(Acinetobacter or mima or mimae or herellea or acinetobacterium):ti,ab,kw (Word variations have been searched)

MeSH descriptor: [Proteus] explode all trees

Proteus:ti,ab,kw (Word variations have been searched)

MeSH descriptor: [Serratia] explode all trees

Serratia:ti,ab,kw (Word variations have been searched)

MeSH descriptor: [Citrobacter freundii] explode all trees

((Citrobacter near/1 freundii) or (bacterium near/1 freundii) or (Escherichia near/1 freundii)):ti,ab,kw (Word variations have been searched)

MeSH descriptor: [Morganella morganii] explode all trees

((bacillus near/1 morgan$) or (bacterium near/1 morgana) or (morganella near/1 morgagni$) or (morganella near/1 morganii) or (proteus near/1 morgagni) or (proteus near/1 morgana) or (salmonella near/1 morgana)):ti,ab,kw (Word variations have been searched)

#22  (multiresistant or (multi near/1 resistan$)):ti,ab,kw (Word variations have been searched)

MeSH descriptor: [Drug Resistance, Multiple] explode all trees

#23  #22 or #23

MeSH descriptor: [Colistin] explode all trees

#26  (belcomycin or colicort or colimycin$ or colisitin or colisticin or Colistin or colistine or colomycin or (coly near/1 mycin) or colymycin or colymycin or coly-mycin or multimycin or (Polymyxin near/1 E) or totazina):ti,ab,kw (Word variations have been searched)

MeSH descriptor: [Carbapenems] explode all trees

#28  (Carbapenem$ or doripenem or ertapenem or Imipemide or Imipenem or Invanoz or Invanz or meropenem or Merrem or 'MK 0787' or MK0787 or MK-0787 or N Formimidoylthienamycin or N-Formimidoylthienamycin or Penem or Ronem or S 4661 or S-4661 or SM 7338 or SM-7338 or Thienamycin$):ti,ab,kw (Word variations have been searched)

MeSH descriptor: [Piperacillin] explode all trees

#30  (acopex or avocin or cl 227,193 or Cl 227193 or cl 227193 or cl227,193 or Cl227193 or cl227193 or Cl-227193 or Cl-227193 or cl-227193 or cypercil or hishiyadorin or ivacin or pentcillin or pentocillin or picillin$ or pipcil or pipera hameln or pipercap or pipercillin$ or pipercin or pipera-hameln or pipercillin or piperrilline or pipraci$ or pipraks or pipril or piprilin or pitamycin or t 1220 or tl1220 or t-1220 or taiperacillin):ti,ab,kw (Word variations have been searched)

#31  (cl 307579 or cl298741 or cl307579 or tazabactam or tazobac$ or tazocel or tazocillin$ or tazocin or tazomax or tazonam or tazopril or yp 14 or yp14 or ytr 830 or ytr 830h or ytr830 or ytr830h or zosyn):ti,ab,kw (Word variations have been searched)
MeSH descriptor: [Amoxicillin-Potassium Clavulanate Combination] explode all trees

(aclam or aktil or ambilan or amoca or amoclan or amoclav or amoksiklav or amolanic or amometin or (amox near/1 clav) or amox-clav or (amoxi near/1 plus) or (amoxNear/3clavulan$) or amoxiclav or amoxiclav-bid or amoxiclav-teva or amoxiklavl or amoxilin or (amoxicillin-clavulanic near/1 acid) or ancla or (auctalin near/1 duo) or augamox or augmaxcil or augmentan or augmentin$ or augmex or augpen or (augucillin near/1 duo) or auguric or ausclav or auspilic or bactiv or bactoclav or bioclav or (brl near/1 '25000') or brl25000 or brl-25000 or cavumox or ciblor or (clacillin near/1 duo) or clamax or clamentin or clamobit or clamonex or clamovid or clamoxin or (clamoxyl near/1 duo$) or clarubactin or clavamox or clavalar or clavate or clavaxil or (clavamox near/1 plus) or clavubactin or clavudale or clavulanate-amoxicillin or clavulin or (clavulox near/1 duo) or clavumox or (co near/1 amoxiclav) or (co near/1 amoxyclav) or coamoxiclav or co-amoxiclav or coamoxyclav or (cramon near/1 duo) or (croanan near/1 duo) or curam or danoclav or (darzitil near/1 plus) or e-moxclav or enhancin or fleming or fugentin or (fullicilina near/1 plus) or gumentin or hibiotic or inciclav or kamonex or kmosil or lactamox or lansiclav or moxiclav or moxyclav or natravox or nufaclav or palentin or quali-mentin or ranclav or spektramox or stacillin or suplentin or synermox or synermyx or velamox or (velamox near/1 cl) or vestaclav or viaclav or vulamox or xiclav or (zami near/1 '8503'));ti,ab,kw (Word variations have been searched)

((brl near/1 '17421') or brl17421 or (thiophenemalonamic near/1 acid) or negaban or temocillin or temopen);ti,ab,kw (Word variations have been searched)

tigecycline or (tbg near/1 mino) or tygacil or gar 936 or gar936 or (tert near/1 butylglycinamido$));ti,ab,kw (Word variations have been searched)

MeSH descriptor: [Quinolones] explode all trees

((chinolone near/1 derivative) or fluoroquinolones or (haloquinolone near/1 derivative) or ketoquinolines or o xoquinolines or quinolinones or quinolones);ti,ab,kw (Word variations have been searched)

MeSH descriptor: [Aminoglycosides] explode all trees

(adelanin or alcomicin or apigent or apogen or apoten or azupel or bactiderm or biogaracin or bistan or cidomycin or danigen or dermogen or dianfarma or dispagent or duragentam$ or epigent or (friese near/1 gent) or garabiatic or garalone or garamicin$ or garamycin or garbilin or gencin or gendril or genoptic or genrex or gensumycin or gentabiotic or gentabiox or gentac or gentacidin or gentacin or gentacor or gentacycol or gentacyl or gentafair or gentagram or gentak or gental or gentaline or gentalline or gentalol or gentalyn or gentamax or gentame$ or gentamicin$ or gentamina or gentamycin$ or gentamyl or gentamytrex or gentaplus or gentarad or
gentasil or gentasol or gentasone or gentasporin or gentatrim or gentavet or genticin or genticyn or gentiderm or gentimycin or gentocin or gentogram or gentomycin or genum or geomycine or gevramycin or g-mycin or gmyticin or g-myctin or grammicin or hexamycin or jenamicin or konigen or lacromycin or lisagent or martigenta or migenta or miragenta or miramycin or nichogencin or nsc 82261 or nsc82261 or obogen or ocugenta or ocu-mycin or oftagen or ophtagram or optigen or optigen-t or ottogenta or pyogenta or refobacin or ribomicin or rigaminol or rocy gen or rovixida or rupegen or sagesstam or sch 9724 or sch9724 or sedanazin or servigenta or skinfect or sulmycin or tangyn or u-gencin or versigen or yectamicina):ti,ab,kw (Word variations have been searched)

#42 MeSH descriptor: [Amikacin] explode all trees

#43 (akacin or akicin or amicacina or amicasil or amicin or amiglymide v or amikacin$ or amikafur or amikalem or amikan or amikayect or amikin or amiklin or amikozi$ or amikatam or amitracin or amixin or amukin or apalin or bb k 8 or bb k8 or bbb 8 or bb-k 8 or bbb8 or bbk 8 or bb-k8 or biciin or bicklin or biokacin or briclin or briklin or chemacin or cinmik or fabianol or gamikal or glukanin or kacinth-a or kanbine or kormakin or likacin or lukadin or miacin or mikasome or onikin or oprad or orlobin or pediakin or riklinak or savox or selema or solselx or solseymcin or sulfate amikacin or tybikin or vs 107 or vs107 or yectamid):ti,ab,kw (Word variations have been searched)

#44 MeSH descriptor: [Fosfomycin] explode all trees

#45 (fosfocil or fosfocin or fosfocina or fosfomicin or fosfomycin or fosfonomycin or ‘mk 0955’ or mk 955 or mk0955 or mk955 or monuril or phosphomycin or phosphonomycin):ti,ab,kw (Word variations have been searched)

#46 MeSH descriptor: [Aztreonam] explode all trees

#47 (az near/1 threonam) or azactam or azenam or azthreonam or aztrenonam or (corus near/1 ‘1020’) or dynabiotic or primbactam or SQ 26,776 or sq 26,776 or sq 26776 or SQ-26,776 or sq26776 or sq-26776 or urobactam):ti,ab,kw (Word variations have been searched)

#48 MeSH descriptor: [Nitrofurantoin] explode all trees

#49 (berkfurin or biofurin or chemiofuran or dantafur or f 30 or f30 or fua-med or furaben or furadantin$ or furadantoin or furadina or furadoine or furadonin or furadonine or furalan or furanpur or furantocmpren or furantoin$: or furobactina or furofen or furophen or infurin or ituran or ivadantin or macrobid or macrodantin$: or macrofurin or macrofurin or micofurantin$: or mitofuratoin or nephrenex or nifurin or nifuryl or (nitro near/1 macro) or nitrofuracin or nitrofuradantoin or nitrofurantine or nitrofurantoin$: or nitrofurin or novofuran or nsc 2107 or nsc2107 or orafuran or parfurin or phenurin or (potassium near/1 furagin) or ralodantin or trocurine or urantin or (uro near/1 tablinen) or urodil or urodis or urofuran or urolong or urotablinen or uro-tablinen or urotoina or uvmacin):ti,ab,kw (Word variations have been searched)

#50 MeSH descriptor: [Cephalosporins] explode all trees

#51 ((Cephalosporanic near/1 Acid$) or Cephalosporin$ or Cefamandole or Cefoperazone or Cefazolin or Cefonicid or Cefsulodin or Cephaetrite or Cefotaxime or Cephalothin or Cephapirin or Cephalexin or Cefaclor or Cefadroxil or Cephaloglycin or
Cephradine or Cephaloridine or Ceftazidime or Cephapline or Cefotetan or Cefoxitin):ti,ab,kw (Word variations have been searched)

#52 MeSH descriptor: [Amdinocillin Pivoxil] explode all trees

#53 ((amdinocillin near/1 pivoxil) or (FL near/1 ‘1039’) or FL1039 or FL-1039 or pivamidocillin or Pivmecillinam or Selexid or coactabs or (ro near/1 ‘109071’) or (ro10 near/1 ‘9071’) or ro109071):ti,ab,kw (Word variations have been searched)

#54 #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53

#55 #21 and #24 and #54 (21)

4.2.3. Embase (January 1980 to December 2012)

1 exp Escherichia coli/ (255846)

2 (Eaggec or (escherichia adj coli) or (e adj coli) or (alkalescens-dispar adj group) or (bacillus adj escherichii) or (Coli adj bacillus) or (Coli adj bacterium) or colibacillus or (colon adj bacillus)).ti,ab. (240749)

3 exp Klebsiella/ (30199)

4 (klebsiella or Calymmatobacterium or (aerobacter adj aerogenes) or ((bacillus or bacterium) adj pneumonia) or ((friedlaender or Friedlander) adj bacillus) or (Hyalococcus adj pneumonia) or Pneumobacillus).ti,ab. (22836)

5 ('k. pneumoniae' or 'b. friedlander').ti,ab. (5513)

6 exp Enterobacter/ (12784)

7 (enterobacter or aerobacter).ti,ab. (9700)

8 exp Pseudomonas aeruginosa/ (55073)

9 ((bacillus adj pyocyaneus) or (bacterium adj (aeruginosum or pyocyaneum)) or (blue adj apus) or (Pseudomonas adj (aeruginosa or aureofaciens or pyoceaneus or pyocyanea or pyocyaneus))).ti,ab. (43474)

10 'p. aeruginosa'.ti,ab. (17572)

11 exp Acinetobacter/ (12028)

12 (Acinetobacter or mima or mimae or herellea or acinetobacterium).ti,ab. (10917)

13 exp Proteus/ (14447)

14 Proteus.ti,ab. (10461)

15 exp Serratia/ (9507)

16 Serratia.ti,ab. (7407)

17 exp Citrobacter freundii/ (1778)

18 ((Citrobacter adj freundii) or (bacterium adj freundii) or (Escherichia adj freundii)).ti,ab. (1675)

19 exp Morganella morganii/ (1134)
20 ((bacillus adj morgan$) or (bacterium adj morgana) or (morganella adj morgagni$) or (morganella adj morganii) or (proteus adj morgagni) or (proteus adj morgana$) or (salmonella adj morgana)).ti,ab. (804)

21 or/1-20 (396800)

22 (multiresistant or (multi adj resistan$)).ti,ab. (5599)

23 exp multidrug resistance/ (29629)

24 22 or 23 (33705)

25 exp Colistin/ (8049)

26 (belcomycin or colicort or colimycin$ or colisitin or colisticin or Colistin or colistine or colomycin or (coly adj mycin) or colymicin or colymycin or coly-mycin or multimycin or (Polymyxin adj E) or totazina).ti,ab. (3104)

27 exp Carbapenems/ (4745)

28 (Carbapenem$ or doripenem or ertapenem or Imipemide or Imipenem or Invanz or Invanz or meropenem or Merrem or 'MK 0787’ or MK0787 or MK-0787 or N Formimidoylthienamycin or N-Formimidoylthienamycin or Penem or Ronem or S 4661 or S-4661 or SM 7338 or SM-7338 or Thienamycin$).ti,ab. (18086)

29 exp Piperacillin/ (14822)

30 (acopex or avocin or cl 227,193 or Cl 227193 or cl 227193 or cl 227,193 or Cl227193 or cl227193 or Cl-227193 or cl-227193 or cypercil or hishiyaclorin or ivacin or penticillin or pentocillin or picillin$ or pipcil or pipera hameln or piperacil or piperacillin$ or piperacine or pipera-hameln or pipericillin or piperilline or pipracti$ or pipraks or pipril or piprilin or pitamycin or t 1220 or t1220 or t-1220 or taiperacillin).ti,ab. (6462)

31 exp Amoxicillin-Potassium Clavulanate Combination/ (23616)

32 (aclam or aktil or ambilan or amocla or amoclan or amoclav or amoksiklav or amolanic or amometin or (amox adj clav) or amox-clav or (amoxi adj plus) or (amox adj j clavulan$) or amoxiclav or amoxiclav-bid or amoxiclav-teva or amoxiklav or amoxdin or (amoxycillin-clavulanic adj acid) or ancla or (auclatin adj duo) or augamox or augmaxcil or augmentan or augmentin$ or augmex or augpen or (augucillin adj duo) or augurcin or ausclav or auspilic or bactiv or bactoclav or bioclavid or (brl adj ‘25000’) or brl25000 or brl-25000 or cavumox or ciblor or (clacillin adj duo) or clamax or clamentin or clamobit or clamonex or clamoid or clamoxin or (clamoxyl adj duo$) or clarin-duo or clavamox or clavar or clavinex or clavodar or clavoxil or (clavoxilin adj plus) or clavubactin or clavudale or clavulanate-amoxicillin or clavulin or (clavulox adj duo) or clavumox or (co adj amoxiclav) or (co adj amoxyclav) or coamoxiclav or co-amoxiclav or coamoxyclav or (cramon adj duo) or (croanan adj duo) or curam or danoclav or (darzitin adj plus) or e-moxclav or enhancin or fleming or fugentin or (fullicilina adj plus) or gumentin or hibiotic or incidiv cl klonex or kloxilin or lactamox or lansiclav or moxiclav or moxicle or moxyclav or natravox or nufaclov or palentin or quali-mentin or ranclav or spektramox or stacillin or suplentin or synermix or synulox or (velamox adj cl) or vestaclav or viaclav or vulamox or xiclav or (zami adj ‘8503’)).ti,ab. (11598)

33 exp Quinolones/ (101072)
(chino\-lone \ adj \ derivative) \ or \ fluoroquinolones \ or \ (haloquinolone \ adj \ derivative) \ or \ ketoquinolines \ or \ oxoquinolines \ or \ quinolinones \ or \ quinolones).ti,ab. (15677)

35 \ exp \ Aminoglycosides/ \ (10599)

36 (Aminoglycosides \ or \ Anthracyclines \ or \ Aclarubicin \ or \ Daunorubicin \ or \ Plicamycin \ or \ Butirosin \ Sulfate \ or \ Sisomicin \ or \ Hygromycin \ B \ or \ Kanamycin \ or \ Dibekacin \ or \ Nebramyacin \ + \ or \ Metrizamide \ or \ Neomycin \ or \ Framycetin \ or \ Paromomycin \ or \ Ribostamycin \ or \ Puromycin \ or \ Spectinomycin \ or \ Streptomycin \ or \ Dihydrostreptomycin \ Sulfate \ or \ Strepto"thricins \ or \ Streptozocin).ti,ab. (56708)

37 \ exp \ Gentamicins/ \ (70647)

38 (adelanin \ or \ alcomicin \ or \ apigent \ or \ apogen \ or \ apoten \ or \ azupel \ or \ bactiderm \ or \ biogaracnic \ or \ bristagen \ or \ cidomycin \ or \ danigen \ or \ dermogen \ or \ di"nafarma \ or \ dis"pagent \ or \ duragentam$ \ or \ epigent \ or \ (frieso \ adj \ gent) \ or \ garabi"otic \ or \ garalone \ or \ garmicin$ \ or \ garamycin \ or \ garbilocin \ or \ gencin \ or \ gendril \ or \ genoptic \ or \ genrex \ or \ gensumycin \ or \ genta"biotic \ or \ gentabiox \ or \ gentac \ or \ gentacicin \ or \ gentacin \ or \ gentacor \ or \ gentacycol \ or \ gentacly \ or \ gentafair \ or \ gentagram \ or \ gentak \ or \ gental \ or \ gentaline \ or \ gentalline \ or \ gentalol \ or \ gentam\-x \ or \ gentame$ \ or \ gentamycin$ \ or \ gentam"na \ or \ gentamycin$ \ or \ gentamyl \ or \ gentamytrex \ or \ gentaplus \ or \ gentarad \ or \ gentasil \ or \ gentasol \ or \ gentasone \ or \ gentasporin \ or \ gentatrium \ or \ gentavet \ or \ genticin$ \ or \ genticyn \ or \ gentiderm \ or \ gentimycin \ or \ gentocin \ or \ gentogram \ or \ gentomy"cin \ or \ genum \ or \ geomycin \ or \ gevramycin \ or \ g-mycin \ or \ gmy"tacin \ or \ g-myticin \ or \ grammicin \ or \ hexamycin \ or \ jenamicin \ or \ konigen \ or \ lacromycin \ or \ lisagent \ or \ martigna\-ta \ or \ migenta \ or \ miragenta \ or \ miramycin \ or \ nichogencin \ or \ nsc 82261 \ or \ nsc82261 \ or \ obogen \ or \ ocugenta \ or \ ocu-mycin \ or \ oftagan \ or \ optagram \ or \ optagena \ or \ optigen \ or \ optique \ or \ ottogen \ or \ pyogenta \ or \ refo"bacin \ or \ ribomicin \ or \ rigaminol \ or \ rocy \ gen \ or \ rovixida \ or \ rupegen \ or \ sagentam \ or \ sch 9724 \ or \ sch9724 \ or \ sedanazin \ or \ servigenta \ or \ skinfect \ or \ sulmycin \ or \ tangyn \ or \ u-gencin \ or \ versigen \ or \ yectamicina).ti,ab. (23700)

39 \ exp \ Amikacin/ \ (28644)

40 (akacin \ or \ akicin \ or \ amicacina \ or \ amicasil \ or \ amicin \ or \ amiglymide \ v \ or \ amikacin$ \ or \ amikafur \ or \ amikalem \ or \ amikan \ or \ amikayect \ or \ amikin \ or \ amikozit \ or \ amiktam \ or \ amitracinc \ or \ amixin \ or \ amukin \ or \ apalin \ or \ bb k 8 \ or \ bb k 8 \ or \ bbk 8 \ or \ bb-k 8 \ or \ bbk8 \ or \ bbk-8 \ or \ bb-k 8 \ or \ b"clicin \ or \ biclin \ or \ biocin \ or \ briklin \ or \ briclin \ or \ briklin \ or \ chemacin \ or \ cinmik \ or \ fabianol \ or \ gamikal \ or \ glukamin \ or \ kacinth-a \ or \ kambine \ or \ kormakin \ or \ likacin \ or \ lukadin \ or \ micain \ or \ mikasome \ or \ onikin \ or \ oprad \ or \ orlobin \ or \ pediakin \ or \ pierami \ or \ riklinak \ or \ savox \ or \ selaxa \ or \ selemycin \ or \ sulfate \ amikacin \ or \ tybikin \ or \ vs 107 \ or \ vs107 \ or \ yectamid).ti,ab. (9841)

41 \ exp \ Fosfomycin/ \ (5561)

42 (fosfo"cil \ or \ fosfocin \ or \ fosfocina \ or \ fosfomicin \ or \ fosfomycin \ or \ fosfonamycin \ or \ ‘mk 0955’ \ or \ mk 955 \ or \ mk0955 \ or \ mk955 \ or \ mon"ril \ or \ phosphomycin \ or \ phosphonomycin).ti,ab. (2386)

43 \ exp \ Azt"reonam/ \ (10567)

44 (az \ adj \ threonam) \ or \ azactam \ or \ azenam \ or \ azthreonam \ or \ azt"reonam \ or \ (corus \ adj \ ‘1020’) \ or \ dynabiotic \ or \ primbactam \ or \ SQ 26,776 \ or \ sq 26,776 \ or \ sq 26776 \ or \ SQ-26,776 \ or \ sq26776 \ or \ sq-26776 \ or \ uro"bactam).ti,ab. (3245)

45 \ exp \ Nitrofurantoin/ \ (9724)
46 (berkfurin or biofurin or chemiofuran or dantafur or f30 or f30 or fua-med or furaben or furadantin$ or furadantoin or furadina or furadoine or furadonin or furadonine or furalan or furanpur or furantocompen or furantoin$ or furobactina or furofen or furophen or infurin or ituran or ivadantin or macrobif or macrodantin$ or macrofuran or macrofurin or micofurantin$ or mitrofuratoin or nephroxen or nieroifu or nifurantin or nifuryl or (nitro adj macro) or nitrofuracin or nitrofuradantoin or nitrofurante or nitrofurantoin$ or nitofurin or novofuran or nsc 2107 or nsc2107 or orafuran or parfuran or phenurin or (potassium adj furagin) or ralodantin or trocureine or urantin or (uro adj tablinen) or urodi1 or urodisin or urofuran or urolong or urotablinen or uro-tablinen or urotoina or uvamin).ti,ab. (3412)
47 exp Cephalosporins/ (150937)
48 (Axepim$ or bmy 28142 or bmy28142 or BMY-28142 or Cefepim$ or cefepitax or ceficad or cepimax or forzyn beta or maxcef or maxfrom or maxipime or Quadrocef).ti,ab. (2995)
49 exp tazobactam/ (3045)
50 (cl 307579 or cl298741 or cl307579 or tazabactam or tazobac$ or tazocel or tazocillin$ or tazocin or tazomax or tazonam or tazopril or yp 14 or yp14 or ytr 830 or ytr 830h or ytr830 or ytr830h or zosyn).ti,ab. (3809)
51 exp temocillin/ (499)
52 ((brl adj ‘17421’) or brl17421 or (thiophenemalonamic adj acid) or negaban or temocillin or temopen).ti,ab. (236)
53 exp tigecycline/ (3876)
54 (tigecycline or (tbg adj mino) or tygacil or gar 936 or gar936 or (tert adj butylglycinamido$)).ti,ab. (1970)
55 exp cefepime/ (9948)
56 ((Cephalosporanic adj Acid$) or Cephalosporin$ or Cefamandole or Cefoperazone or Cefazolin or Cefonicid or Cefsulodin or Cephacetrile or Cefotaxime or Cephapirin or Cephalexin or Cefaclor or Cefadroxil or Cefadroxil or Cefalphycin or Cephadrine or Cephaloridine or Ceftazidine or Cephamin or Cefmetazole or Cefotetan or Cefoxitin).ti,ab. (45983)
57 exp pivmecillinam/ (685)
58 ((amdinocillin adj pivoxil) or (FL adj ‘1039’) or FL1039 or fl1039 or FL-1039 or pivamdinocillin or Pivmecillinam or Selexid or coactabs or (ro adj ‘109071’) or (ro10 adj ‘9071’) or ro109071).ti,ab. (280)
59 or/25-58 (349366)
60 21 and 24 and 59 (4969)
61 (review or review,tutorial or review, academic).pt. (1901059)
62 (systematic$. adj5 review$).tw,sh. (70959)
63 (systematic$. adj5 overview$).tw,sh. (869)
64 (quantitativ$. adj5 review$).tw,sh. (15516)
65 (quantitativ$. adj5 overview$).tw,sh. (203)
101 (review$ adj10 (papers or trials or trial data or studies or evidence or intervention$ or evaluation$ or outcome$ or findings)).tw. (248295)
102 review.ti. (264011)
103 metanaly$.tw. (316)
104 letter.pt. (800258)
105 editorial.pt. (417835)
106 104 or 105 (1218093)
107 or/61 -103 (2212977)
108 107 not 106 (2200787)
109 (clin$ adj2 trial).mp. (968683)
110 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. (190403)
111 (random$ adj5 (assign$ or allocat$)).mp. (101920)
112 randomi$.mp. (613392)
113 crossover.mp. (59181)
114 exp randomized-controlled-trial/ (334017)
115 exp double-blind-procedure/ (112280)
116 exp crossover-procedure/ (35737)
117 exp single-blind-procedure/ (16758)
118 exp randomization/ (60197)
119 or/109-118 (1282139)
120 intervention?.ti. or (intervention? adj6 (clinician? or collaborat$ or community or complex or DESIGNS or doctor? or educational or family doctor? or family physician? or family practitioner? or financial or GP or general practice? or hospital? or impact? or improv$ or individuali?e? or individuali?ing or interdisciplin$ or multicomponent or multi-component or multidisciplin$ or multi-disciplin$ or multifacet$ or multi-facet$ or multimodal$ or multi-modal$ or personali?e? or personali?ing or pharmacies or pharmacist? or pharmacy or physician? or practitioner? or prescrib$ or prescription? or primary care or professional$ or provider? or regulatory or regulatory or tailor$ or target$ or team$ or usual care)).ab. (175033)
121 (hospital$ or patient?).hw. and (study or studies or care or health$ or practitioner? or provider? or physician? or nurse? or nursing or doctor?).ti,hw. (1363115)
122 demonstration project?.ti,ab. (2081)
123 (pre-post or ‘pre test$’ or pretest$ or posttest$ or ‘post test$’ or (pre adj5 post)).ti,ab. (78013)
124 (pre-workshop or post-workshop or (before adj3 workshop) or (after adj3 workshop)).ti,ab. (673)
125 trial.ti. or ((study adj3 aim?) or ‘our study’).ab. (724065)
126 (before adj10 (after or during)).ti,ab. (394152)
127 (time points adj3 (over or multiple or three or four or five or six or seven or eight or nine or ten or eleven or twelve or month$ or hour? or day? or 'more than')).ab. (10006)

128 pilot.ti. (43036)

129 (multicentre or multicenter or multi-centre or multi-center).ti. (34428)

130 random$.ti,ab. or controlled.ti. (819713)

131 review.ti. (264011)

132 *experimental design/ or *pilot study/ or quasi experimental study/ (5205)

133 ('quasi-experiment$' or quasiexperiment$ or 'quasi random$' or quasirandom$ or 'quasi control$' or quasicontrol$ or ((quasi$ or experimental) adj3 (method$ or study or trial or design$))).ti,ab. (105122)

134 or/120-133 (3341084)

135 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ (18985259)

136 human/ or normal human/ or human cell/ (14037258)

137 135 and 136 (14004971)

138 135 not 137 (4980288)

139 ('time series' adj2 interrupt$).ti,ab. (922)

140 134 not (138 or 139) (2996658)

141 108 or 119 or 140 (5157863)

142 and 141 (1860)

4.2.4. Medline (January 1946 to December 2012)

1 exp Escherichia coli/ (224545)

2 (Eaggec or (escherichia adj coli) or (e adj coli) or (alkalescens-dispar adj group) or (bacillus adj escherichii) or (Coli adj bacillus) or (Coli adj bacterium) or colibacillus or (colon adj bacillus)).ti,ab. (226847)

3 exp Klebsiella/ (13720)

4 (klebsiella or Calycombatobacterium or (aerobacter adj aerogenes) or ((bacillus or bacterium) adj pneumonia) or ((friedlaender or Friedlander) adj bacillus) or (Hyalococcus adj pneumonia) or Pneumobacillus).ti,ab. (18345)

5 ('k. pneumoniae' or 'b. friedlander').ti,ab. (3902)

6 exp Enterobacter/ (5504)

7 (enterobacter or aerobacter).ti,ab. (8130)

8 exp Pseudomonas aeruginosa/ (30232)

9 ((bacillus adj pyocyaneus) or (bacterium adj (aeruginosum or pyocyaneum)) or (blue adj apus) or (Pseudomonas adj (aeruginosa or aureofaciens or pyoceaneus or pyocyanea or pyocyaneus))).ti,ab. (35984)

10 'p. aeruginosa'.ti,ab. (14103)
11 exp Acinetobacter/ (5262)
12 (Acinetobacter or mima or mimae or herellea or acinetobacterium).ti,ab. (8005)
13 exp Proteus/ (8091)
14 Proteus.ti,ab. (9496)
15 exp Serratia/ (5505)
16 Serratia.ti,ab. (6720)
17 exp Citrobacter freundii/ (438)
18 ((Citrobacter adj freundii) or (bacterium adj freundii) or (Escherichia adj freundii)).ti,ab. (1361)
19 exp Morganella morganii/ (133)
20 ((bacillus adj morgan$) or (bacterium adj morgana) or (morganella adj morgagni$) or (morganella adj morganii) or (proteus adj morgagni) or (proteus adj morgana$) or (salmonella adj morgana)).ti,ab. (601)
21 or/1-20 (360253)
22 (multiresistant or (multi adj resistan$)).ti,ab. (3949)
23 exp drug resistance, multiple/ (21763)
24 22 or 23 (24405)
25 exp Colistin/ (2107)
26 (belcomycin or colicort or colimycin$ or colisitin or colisticin or Colistin or colistine or colomycin or (coly adj mycin) or colymicin or coly-mycin or multimycin or (Polymyxin adj E) or totazina).ti,ab. (2346)
27 exp Carbapenems/ (6668)
28 (Carbapenem$ or doripenem or ertapenem or Imipemide or Imipenem or Invanz or Invanz or meropenem or Merrem or ‘MK 0787’ or MK0787 or MK-0787 or N Formimidoylthienamycin or N-Formimidoylthienamycin or Penem or Ronem or S 4661 or S-4661 or SM 7338 or SM-7338 or Thienamycin$).ti,ab. (11771)
29 exp Piperacillin/ (2035)
30 ((acopex or avocin or cl 227,193 or Cl 227193 or cl 227193 or cl 227193 or cl 227,193 or CI227193 or cl227193 or Cl-227193 or Cl-227193 or cypercil or hishiyadorin or ivacin or pentcillin or pentocillin or picillin$ or pipcil or pipera hameln or piperacil or piperacillin$ or piperacin or pipera-hameln or pipercillin or piperilline or pipraci$ or pipraks or pipril or piprilin or pitamycin or t 1220 or t1220 or t-1220 or taiperacillin).ti,ab. (4319)
31 (cl 307579 or cl298741 or cl307579 or tazabactam or tazobac$ or tazocel or tazocillin$ or tazocin or tazomax or tazonam or tazopril or yp 14 or yp14 or yp 830 or ytr 830h or ytr830 or ytr830h or zosyn).ti,ab. (2217)
32 exp Amoxicillin-Potassium Clavulanate Combination/ (1914)
33 (aclam or aktil or ambilan or amoca or amocl or amoclav or amoksilav or amolanic or amometin or (amox adj clav) or amox-clav or (amoxi adj plus) or (amox adj3 clavulan$) or amoxiclav or amoxiclav-bid or amoxiclav-teva or amoxiklav or
amoxxlin or (amoxycillin-clavulanic adj acid) or ancla or (auclatin adj duo) or augamox or augmaxcil or augmentan or augmentin$ or augmex or augpen or (augucillin adj duo) or augurcin or ausclav or auspilic or bactiv or bactoclav or bioclavid or (brl adj '25000') or brl25000 or brl-25000 or cavumox or ciblor or (clacillin adj duo) or clamax or clamentin or clamobit or clamoxin or (clamoxyl adj duo$) or clarin-duo or clavamox or clavar or clavixin or clavodar or clavoxil or (clavoxilin adj plus) or clavubactin or clavudale or clamulanate-amoxicillin or clavulin or (clavulox adj duo) or clavumox or (co adj amoxiclav) or (co adj amoxyclav) or coamoxiclav or co-amoxiclav or coamoxyclov or (cramon adj duo) or (croanan adj duo) or curam or danoclav or (darzitil adj plus) or e-moxclav or enhancin or fleming or fugentin or (fullicilina adj plus) or gumentin or hibiotic or inciclav or klamonex or kmoxilin or lactamox or lansiclav or moxiclav or moxicle or moxyclav or natravox or nufaclav or palentin or quali-mentin or ranclav or spectramox or stacillin or suplentin or synermox or synulox or (velamox adj cl) or vestacla or viaclav or vulamox or xiclav or (zami adj '8503')).ti,ab. (9184)

34 ((brl adj '17421') or brl17421 or (thiophenemalonamic adj acid) or negaban or temocillin or temopen).ti,ab. (179)

35 (tigecycline or (tbg adj mino) or tygacil or gar 936 or gar936 or (tert adj butylglycinamido$)).ab,ti. (1161)

36 exp Quinolones/ (33277)

37 ((chinolone adj derivative) or fluoroquinolones or (haloquinolone adj derivative) or ketoquino lines or o xoquinolines or quinolinones or quinolones).ti,ab. (11055)

38 exp Aminoglycosides/ (122582)

39 (Aminoglycosides or Anthracyclines or Aclarubicin or Daunorubicin or Plicamycin or Butirosin Sulfate or Sisomicin or Hygromycin B or Kanamycin or Dibekacin or Nebramycin + or Metrizamide or Neomycin or Framycetin or Paromomycin or Ribostamycin or Puromycin or Spectinomycin or Streptomycin or Dihydrostreptomycin Sulfate or Streptothricins or Streptozocin).ti,ab. (52288)

40 exp Gentamicins/ (16678)

41 (adelanin or alcomicin or apigent or apigen or apoten or azupel or bactiderm or biogaracin or bristang or cidimicin or danigen or dermogen or dianarma or dispagent or duragentam$ or epigen or (frieso adj gent) or garbiotic or garalone or garamicin$ or garamycin or garbilocin or gencin or gendril or genoptic or genrex or gensumycin or gentabiotic or gentabiox or gentac or gentacidin or gentac or gentacol or gentacycl or gentafair or gentagram or gentak or genital or gentoline or gentalline or gentalol or gentalyn or gentamax or gentame$ or gentamicin$ or gentamina or gentamycin$ or gentamyl or gentamyxtriex or gentaplus or gentarad or gentasil or gentasol or gentasone or gentasporin or gentatrim or gentavet or gentic$ or genticyn or gentiderm or gentimycin or gentocin or gentogram or gentomycin or genum or geomyicine or gevramycin or g-myicin or gmyticin or g-lyticin or grammicin or hecamycin or jenamicin or konigen or lacromycin or lisagent or martigenta or migenta or miragenta or miramycin or nichogencin or nsc 82261 or nsc82261 or obogen or ocugenta or ouc-myicin or oftagen or ophtagram or ophagen or optigen or opti-genta or ottogen or pyogenta or refobac or ribomicin or rigaminol or rocy gen or rovixida or rupegen or sagestam or sch 9724 or sch9724 or sedanazin or servigenta or skinfect or sulmycin or tangyn or u-gencin or versigen or yectaminica).ti,ab. (19829)
42 exp Amikacin/ (3372)
43 (akacin or akcin or amicacina or amicasil or amicin or amiglymide v or amikacin$ or amikafur or amikalem or amikan or amikayect or amikin or amiklin or amikozit or amiktam or amitracin or amixin or amukin or apalin or bb k 8 or bb k8 or bbk 8 or bb-k 8 or bbk8 or bbk-8 or bb-k8 or bcklin or bcklin or biokacin or briklin or briklin or chemacin or cinmik or fabianol or gamikal or glukamin or kacinh-a or kanbine or kormakin or likacin or lukadin or mikacin or mikasome or onikin or oprad or orlobin or pediakin or pierami or riklinak or savox or selaxa or selemycin or sulfate amikacin or tybikin or vs 107 or vs107 or yectamid).ti,ab. (7140)
44 exp Fosfomycin/ (1378)
45 (fosfocil or fosfocin or fosfocina or fosfomicin or fosfomycin or fosfonomycin or 'mk 0955' or mk 955 or mk0955 or mk955 or monuril or phosphomycin or phosphonomycin).ti,ab. (1779)
46 exp Aztreonam/ (1233)
47 ((az adj threonam) or azactam or azenam or azthreonam or aztreonam or (corus adj '1020') or dynabiotic or primbactam or SQ 26,776 or sq 26,776 or sq 26776 or SQ-26,776 or sq26776 or sq-26776 or urobactam).ti,ab. (2333)
48 exp Nitrofurantoin/ (2253)
49 (berkfurin or biofurin or chemiofuran or dantafur or d 30 or f30 or fia-med or furaben or furadantin$ or furadantoin or furadina or furadoine or furadonin or furadonine or furalan or furanpur or furantocompren or furantoin$ or furapactina or furofen or furophen or infurin or ituran or ivadantin or macrobic or macrodantin$ or macrofurin or macrofurin or macrofurin or macrofurin or macrofurin or macrofurin or macrofurin or macrofurin or macrofurin or macrofurin or macrofurin or macrofurin or macrofurin or macrofurin or macrofurin or macrofurin or macrofurin or nitrofurin or nitrofuracini or nitrofuracin or nitrofuradantoin or nitrofurantoin or nitrofurantoin$ or nitrofurin or novofuran or nsc 2107 or nsc 2107 or orafuran or parfuran or phenurin or (potassium adj furagin) or ralodantin or trocurine or urantin or (uro adj tablinen) or urodil or urodin or urofuran or urolong or urotablinen or uro-tablinen or urotoina or uvamin).ti,ab. (2721)
50 exp Cephalosporins/ (35352)
51 (Axepim$ or bmy 28142 or bmy28142 or BMY-28142 or Cefepim$ or cefepitax or cefpid or cepimax or forzyn beta or maxcef or maxfom or maxipime or Quadrocef).ti,ab. (1916)
52 ((Cephalosporanic adj Acid$) or Cephalosporin$ or Cefamandole or Cefoperazone or Cefazolin or Cefonicid or Cefsulodin or Cefpodoxime or Cefotaxime or Cephalothin or Cepahapirin or Cephalixin or Cefaclor or Cefadroxil or Cephaloglycin or Cephradine or Cephaloridine or Ceftazidime or Cephamycins or Cefmetazole or Cefotetan or Cefoxitin).ti,ab. (35099)
53 exp Amdinocillin Pivoxil/ (199)
54 ((amdinocillin adj pivoxil) or (FL adj '1039') or FL1039 or FL1039 or FL-1039 or pivamdinocillin or Pivmecillinam or Selexid or coactabs or (ro adj '109071') or (ro10 adj '9071') or ro109071).ti,ab. (237)
55 or/25-54 (246506)
56 21 and 24 and 55 (3195)
57 exp clinical trial/ (706293)
58 exp randomized controlled trials/ (85563)
59 exp double-blind method/ (118498)
60 exp single-blind method/ (17086)
61 exp cross-over studies/ (30990)
62 randomized controlled trial.pt. (342334)
63 clinical trial.pt. (476450)
64 controlled clinical trial.pt. (85694)
65 (clinic$ adj2 trial).mp. (552367)
66 (random$ adj5 control$ adj5 trial$).mp. (443104)
67 (crossover or cross-over).mp. (59003)
68 ((singl$ or double$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. (162179)
69 randomi$.mp. (509202)
70 (random$ adj5 (assign$ or allocat$ or assort$ or reciev$)).mp. (150717)
71 or/57-70 (968331)
72 (review or review, tutorial or review, academic).pt. (1758734)
73 (systematic$ adj5 review$).tw,sh. (40365)
74 (systematic$ adj5 overview$).tw,sh. (663)
75 (quantitativ$ adj5 review$).tw,sh. (3684)
76 (quantitativ$ adj5 overview$).tw,sh. (153)
77 (quantitativ$ adj5 synthesis$).tw,sh. (1107)
78 (methodologic$ adj5 review$).tw,sh. (2696)
79 (methodologic$ adj5 overview$).tw,sh. (180)
80 (integrative research review$ or research integration).tw. (78)
81 meta-analysis as topic/ (12608)
82 (meta-analys$ or meta analys$ or metaanalys$).tw,sh. (62359)
83 (meta synthesis or meta synthesis or metasynthesis).tw,sh. (215)
84 (meta-regression or meta regression or metaregression).tw,sh. (1650)
85 meta-analysis.pt. (37918)
86 (synthes$ adj3 literature).tw. (1070)
87 (synthes$ adj3 evidence).tw. (2956)
88 integrative review.tw. (583)
89 data synthesis.tw. (6328)
90 (research synthesis or narrative synthesis).tw. (463)
91 (systematic study or systematic studies).tw. (5679)
92 systematic comparison$\text{.tw. (953)}$
93 systematic comparison$.tw. (953)
94 evidence based review$\text{.tw. (965)}$
95 comprehensive review$.tw. (5290)
96 critical review$\text{.tw. (9227)}$
97 quantitative review$\text{.tw. (382)}$
98 structured review$\text{.tw. (376)}$
99 realist review$\text{.tw. (24)}$
100 realist synthesis$\text{.tw. (11)}$
101 review$\text{.ti. (212126)}$
102 (review$\text{ adj4 (papers or trials or studies or evidence or intervention$ or evaluation$)}$).tw. (80949)
103 metanaly$.tw. (137)
104 letter$\text{.pt. (766872)}$
105 editorial$\text{.pt. (310993)}$
106 comment$\text{.pt. (493546)}$
107 or/104-106 (1166749)
108 or/72-103 (1897061)
109 108 not 107 (1860495)
110 intervention$\text{.ti. or (intervention? adj6 (clinician? or collaborat$ or community or complex or DESIGN$ or doctor? or educational or family doctor? or family physician? or family practitioner? or financial or GP or general practice? or hospital? or impact? or improv$ or individuali?e? or individuali?ing or interdisciplin$ or multicomponent or multi-component or multidisciplin$ or multi-disciplin$ or multifacet$ or multi-facet$ or multimodal$ or multi-modal$ or personali?e? or personali?ing or pharmacists or pharmacist? or pharmacy or physician? or practitioner? or prescrib$ or prescription? or primary care or professional$ or provider? or regulatory or regulatory or tailor$ or target$ or team$ or usual care$)).ab. (128957)$
111 (pre-intervention? or preintervention? or ‘pre intervention?’ or post-intervention? or postintervention? or ‘post intervention?’).\text{ti,ab. (7451)}$
112 demonstration project?.\text{ti,ab. (1742)}$
113 (pre-post or ‘pre test$’ or pretest$ or posttest$ or ‘post test$’ or (pre adj5 post)).\text{ti,ab. (52427)}$
114 (pre-workshop or post-workshop or (before adj3 workshop) or (after adj3 workshop)).\text{ti,ab. (472)}$
115 trial\text{.ti. or ((study adj3 aim?) or ‘our study’)).ab. (500725)}$
116 (before adj10 (after or during)).\text{ti,ab. (314768)}$
117 (‘quasi-experiment$’ or quasiexperiment$ or ‘quasi random$’ or quasirandom$ or ‘quasi control$’ or quasicontrol$ or ((quasi$ or experimental) adj3 (method$ or study or trial or design$))).ti,ab,hw. (84783)
118 (‘time series’ adj2 interrupt$).ti,ab,hw. (744)
119 (time points adj3 (over or multiple or three or four or five or six or seven or eight or nine or ten or eleven or twelve or month$ or hour? or day? or ‘more than’)).ab. (7043)
120 pilot.ti. (32084)
121 Pilot proj (74648)
122 (clinical trial or controlled clinical trial or multicenter study).pt. (595489)
123 (multicentre or multicenter or multi-centre or multi-center).ti. (24301)
124 random$.ti,ab. or controlled.ti. (624993)
125 (control adj3 (area or cohort? or compare? or condition or design or group? or intervention? or participant? or study)).ab. not (controlled clinical trial or randomized controlled trial).pt. (342332)
126 ‘comment on’.cm. or review.ti,pt. or randomized controlled trial.pt. (2652864)
127 (rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine or animal?).ti. (1254855)
128 exp animals/ not humans.sh. (3812817)
129 (or/110-126) not (or/127-128) (3811646)
130 71 or 109 or 129 (4107075)
131 and 130 (822)
### 4.3.1. Antibiotic stewardship

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Objective and participants</th>
<th>MDR Gram-negative bacteria</th>
<th>Intervention, control and follow-up</th>
<th>Results</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ben-David 2010 ITS</td>
<td>To assess the effect of an intensified intervention, that included active surveillance, on the incidence of infection with carbapenem-resistant <em>K. pneumoniae</em></td>
<td>Bacteria: <em>K. pneumoniae</em></td>
<td>Intervention&lt;br&gt;1. Enhanced national infection control programme: contact precautions were used for the care of all patients with CRKP colonization or infection; the prevalence of colonization or infection was reported daily, and this information was mailed to the hospital management and the national coordinator; and patients infected with CRKP had their names entered into a database so that they could be identified at hospital re-admission&lt;br&gt;2. Active surveillance programme: obtaining rectal culture samples from patients hospitalized in ICUs and in step-down units, at admission to the unit and once weekly until the patient was discharged&lt;br&gt;&lt;br&gt;<strong>Length of pre-intervention:</strong> 17 months prior&lt;br&gt;<strong>Length of post-intervention:</strong> 19 months following</td>
<td>Infection control&lt;br&gt;Before the intervention, the incidence of clinical infection with CRKP had increased 6.42-fold to 6.93 cases per 10,000 patient-days&lt;br&gt;After an enhanced infection control and active surveillance programme was introduced, the incidence of clinical infection reduced to 1.8 cases per 10,000 patient-days (<em>P</em>&lt;0.001). The slope significantly changed with the introduction of the intervention from 0.12 to -0.07 (<em>P</em>&lt;0.001)</td>
<td>Protection against secular changes (high quality)</td>
</tr>
<tr>
<td>Borer 2011 ITS</td>
<td>To devise a local strategy for eradication of a hospital-wide outbreak caused by CRKP</td>
<td>Bacteria: <em>K. pneumoniae</em></td>
<td>Intervention&lt;br&gt;1. Emergency department flagging system</td>
<td>Bacterial colonization and infection</td>
<td>Protection against detection bias (acceptable quality)</td>
</tr>
<tr>
<td>Setting</td>
<td>Objective and participants</td>
<td>MDR Gram-negative bacteria</td>
<td>Intervention, control and follow-up</td>
<td>Results</td>
<td>Quality assessment</td>
</tr>
<tr>
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</tr>
<tr>
<td>Tertiary (one hospital) Israel May 2006–May 2010</td>
<td><strong>Participants</strong> N=803 Adolescents 13–18 years, adults 19–45 years, middle aged 46–64 years, elderly 80+years Male: 410, female: 393 Inclusion criteria: data from medical records of patients with CRKP infection Exclusion criteria: not reported</td>
<td><strong>Resistant to:</strong> carbapenems <strong>Mechanism of resistance:</strong> not reported</td>
<td>2. Building of a cohort space or ward 3. Intensive active surveillance in high-risk wards 4. Epidemiological investigations 5. Carbapenem-restriction policy</td>
<td>During the intervention, the CRKP undetected ratio showed a significant increase from 55.7% for June–December 2007 to 71.2% in 2008, 78.9% in 2009 and 92.5% for February–May 2010 (P≤0.001). From May 2006 through April 2007 (pre-intervention), the CRKP-IN incidence density per 10,000 patient-days was 5.26. After the intervention programme was introduced, the incidence of clinical CRPK infection reduced to 2.91 cases per 10,000 patient-days (P&lt;0.001) in 12/2007, 1.91 in 12/2008 and 1.28 in 12/2009. The slope changed significantly with the introduction of the intervention (P=0.004).</td>
<td>Protection against secular changes (high quality)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Length of pre-intervention:</strong> 11 months prior <strong>Length of post-intervention:</strong> 36 months following</td>
<td></td>
<td>Protection against detection bias (acceptable to low quality)</td>
</tr>
<tr>
<td>Church 2011 ITS</td>
<td>To assess the possible effects of varying usage of levofloxacin, gatifloxacin and moxifloxacin on <em>P. aeruginosa</em> susceptibility to piperacillin-tazobactam, cefepime and tobramycin</td>
<td><strong>Bacteria:</strong> <em>P. aeruginosa</em> <strong>Resistant to:</strong> aminoglycosides (tobramycin), cephalosporins (cefepime), piperacillin/tazobactam</td>
<td><strong>Intervention</strong> 1. Levofloxacin replaced with gatifloxacin in 2001 2. Gatifloxacin replaced with moxifloxacin in 2006 Ciprofloxacin available throughout study period</td>
<td><strong>Antibiotic resistance and susceptibility</strong> No association between the susceptibility of <em>P. aeruginosa</em> isolates to tobramycin and formulary changes was noted. With cefepime, a significant change in susceptibility was detected after the introduction of gatifloxacin (P=0.0099) and</td>
<td>Protection against secular changes (low quality) Protection against detection bias (low quality)</td>
</tr>
<tr>
<td>Objective and participants</td>
<td>MDR Gram-negative bacteria</td>
<td>Intervention, control and follow-up</td>
<td>Results</td>
<td>Quality assessment</td>
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<tr>
<td>USA</td>
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<tr>
<td>January 2000-December 2008</td>
<td>Age: not reported</td>
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<td></td>
<td>Male: not reported, female: not reported</td>
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<td></td>
<td>Inclusion criteria: data from clinical microbiology and pharmacy databases of the Medical University of South Carolina Medical Centre</td>
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<td></td>
<td>Exclusion criteria: not reported</td>
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<td></td>
<td>Mechanism of resistance: not reported</td>
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<td>moxifloxacin (P=0.0571). In the case of piperacillin/tazobactam, a positive change in susceptibility over time was detected after introduction of moxifloxacin (P=0.0589). In each analysis, the effect of total fluoroquinolone usage was not significant</td>
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<tr>
<td></td>
<td>Length of pre-intervention: 15 months prior</td>
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<td></td>
<td>Length of post-intervention 1: 60 months</td>
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<td></td>
<td>Length of post-intervention 2: 30 months following</td>
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<tr>
<td>Cohen 2011</td>
<td>To describe the implementation of an institution-wide, multiple-step intervention to curtail the epidemic spread of CRKP</td>
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<tr>
<td>ITS Setting</td>
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<tr>
<td>Tertiary (one hospital)</td>
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<tr>
<td>Israel</td>
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<tr>
<td>March 2006–August 2010</td>
<td>Participants N=33,570</td>
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<td></td>
<td>Age: not reported</td>
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<td></td>
<td>Male: not reported, female: not reported</td>
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<tr>
<td></td>
<td>Inclusion criteria: all patients affected by CRKP</td>
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<tr>
<td></td>
<td>Exclusion criteria: not reported</td>
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<tr>
<td></td>
<td>Bacteria: <em>K. pneumoniae</em></td>
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<tr>
<td></td>
<td>Resistant to: carbapenems</td>
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<tr>
<td></td>
<td>Mechanism of resistance: not reported</td>
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<tr>
<td></td>
<td>Intervention 1.</td>
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<td></td>
<td>Single-room isolation and contact precautions</td>
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<td></td>
<td>2. Cohort of patients and nursing staff, screening of patients in the same room as newly identified carriers of CRKP, and local protocol for continued cohorting of returning patients</td>
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<td>3. Weekly active surveillance in the ICU</td>
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<tr>
<td></td>
<td>4. Active surveillance of patients on admission to the emergency department</td>
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<td></td>
<td>Length of pre-intervention: not reported</td>
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<td>Length of post-intervention 1: 14 months</td>
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<td>Length of post-intervention 2: 39 months</td>
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<td></td>
<td>Length of post-intervention 3: 2 years</td>
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<tr>
<td></td>
<td>Bacterial colonization and infection</td>
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<td></td>
<td>The incidence (total number of cases of in-hospital CRKP acquisition detected by clinical cultures) and weekly point prevalence were reported as the number of cases per 1000 hospital beds</td>
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<tr>
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<td>Incidence was found to change significantly after intervention 2 (06/2007) and 3 (10/2008). Prevalence was found to change significantly only in September 2009 (after intervention 4)</td>
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<td></td>
<td>In the emergency department, the mean rate of compliance with the active surveillance protocol (± SD) was 43% ± 10%</td>
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<td></td>
<td>Protection against secular changes (high quality)</td>
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<td></td>
<td>Protection against detection bias (acceptable to low quality)</td>
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<tr>
<td>Year</td>
<td>Study Type</td>
<td>Setting</td>
<td>Participants</td>
<td>Objective and participants</td>
<td>MDR Gram-negative bacteria</td>
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<tr>
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</tr>
<tr>
<td>Dortch 2011 ITS</td>
<td>Tertiary (one TICU, one SICU) USA</td>
<td>January 2001 – December 2008</td>
<td>Adults 19–45 years, middle aged 46–64 years, aged 65–79 years Male: 14,277, female: 6569</td>
<td>To examine the effect of the antibiotic stewardship programme on the incidence of resistant Gram-negative HAIs</td>
<td>Bacteria: <em>P. aeruginosa</em>, <em>Acinetobacter</em> spp.</td>
</tr>
<tr>
<td>Lewis 2012 ITS</td>
<td>Tertiary (11 ICUs and immediate care units) USA</td>
<td></td>
<td></td>
<td>To examine the effect of restricting ciprofloxacin use on the resistance of nosocomial Gram-negative bacilli, including <em>P. aeruginosa</em>, to group 2 carbapenems in a hospital’s ICUs and intermediate care units</td>
<td>Bacteria: <em>E. aerogenes</em>, <em>E. cloacae</em>, <em>P. aeruginosa</em>, <em>A. baumannii</em></td>
</tr>
</tbody>
</table>
### Objective and participants

<table>
<thead>
<tr>
<th>Month</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 2004–December 2010</td>
<td>Male: not reported, female: not reported</td>
</tr>
</tbody>
</table>

**Inclusion criteria:** all clinical ICU and intermediate care unit specimens (blood, sterile fluid, sputum, urine, wounds and anaerobic specimens) with test results that were positive for *P. aeruginosa*, *E. aerogenes*, *E. cloacae*, *A. baumannii* and *S. maltophilia*. Only nosocomial cases, defined as involving patients who had a hospital length of stay exceeding two days.

**Exclusion criteria:** results of surveillance and environmental sample cultures.

### MDR Gram-negative bacteria

- (cefepime), piperacillin/tazobactam, fluoroquinolones (ciprofloxacin)

**Mechanism of resistance:** not reported

### Intervention, control and follow-up

**Length of post-intervention:** 42 months

### Results

- 2010. Overall, there was a hospital-wide decrease of 18.4% (*P*<0.0001) in the use of antibacterials during the study time.

**Infection**

- There were no changes observed in the number of nosocomial *S. maltophilia* isolates per 10,000 patient-days following the restriction of ciprofloxacin.

**Antibiotic resistance**

- Over the seven-year time period, there was a decrease of 13.7% in the percentage of ciprofloxacin-resistant *P. aeruginosa* isolates that were collected, which equates to a decrease of 3.9% per year (*P*=0.0017). No significant changes was observed in the susceptibilities to the group II carbapenems of nosocomial Enterobacteriaceae or *A. baumannii* isolates.

### Meyer 2009

**ITS**

**Setting** Tertiary (one ICU) Germany

**Participants**

- *N*=3758
- Age: not reported

**Bacteria:** *E. coli*, *K. pneumoniae*, *P. aeruginosa*

**Resistant to:** cephalosporins (third-generation), piperacillin

**Mechanism of resistance:** ESBL

**Intervention**

1. Education programmes for professionals and patients in July 2004
2. Education sessions on antibiotic guidelines were held in the departments of surgery and anaesthesiology
3. Empiric standard therapy for peritonitis and other intra-abdominal infections was

**Antibiotic use**

- Following the implementation of guidelines in a surgical ICU, a significant and sustainable decrease in the use of third-generation cephalosporins of -110.2 DDD/1000 patient-days (95% CI -140.0 to -80.4, *R²*=0.468) was observed. There was a significant reduction in the use of ampicillins (-167.4 DDD/1000, 95% CI -223.8 to -110.9, *R²*=0.378) and in

**ITS Protection against secular changes (high quality)**

**Protection against detection bias (high quality)**
<table>
<thead>
<tr>
<th>Year</th>
<th>Male: not reported, female: not reported</th>
<th>MDR Gram-negative bacteria</th>
<th>Intervention, control and follow-up</th>
<th>Results</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 2006</td>
<td>Inclusion criteria: not reported</td>
<td>switched from third-generation cephalosporins to piperacillin in combination with a beta-lactamase inhibitor. The duration of antibiotic therapy for open fractures was shortened to single-shot pre-operative prophylaxis</td>
<td>the use of imidazoles (94.5 DDD/1000, 95% CI -121.2 to -67.7, ( R^2 = 0.463 ))</td>
<td>Protection against secular changes (high quality)</td>
<td></td>
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<tr>
<td></td>
<td>Exclusion criteria: not reported</td>
<td><strong>Length of pre-intervention</strong>: 30 months</td>
<td></td>
<td>Protection against detection bias (acceptable quality)</td>
<td></td>
</tr>
</tbody>
</table>

**Meyer 2010**

**ITS**

**Setting**
Tertiary (one ICU)
Germany

**January 2002 – December 2006**

To evaluate the impact of a reduced duration of antibiotic prophylaxis for cerebrospinal shunts on total antibiotic use in the ICU and key resistant pathogens

**Participants**

<table>
<thead>
<tr>
<th>N=11,887</th>
<th>Male: not reported, female: not reported</th>
</tr>
</thead>
</table>

**Inclusion criteria: monthly data on antimicrobial use obtained from the computerized pharmacy database. Monthly resistance data collected from the microbiology laboratory.**

**Bacteria:** *E. coli, K. pneumoniae, P. aeruginosa*

**Resistant to:** carbapenems (imipenem), cephalosporins (third-generation)

**Mechanism of resistance:** not reported

<table>
<thead>
<tr>
<th><strong>Intervention</strong></th>
<th><strong>Antibiotic use</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in antibiotic prophylaxis: Revised recommendation of single-shot prophylaxis with cefuroxime for shunt catheters, beginning in January 2004</td>
<td>Following the implementation of a comprehensive teaching session on antibiotic prophylaxis in cerebrospinal shunts in a surgical ICU, pre-operative prophylaxis for shunt catheters was changed into single-shot prophylaxis, and total antibiotic use decreased (−147.3 DDD/1000 patient-days, ( P=0.052 )). This corresponded to a decrease of 15% in the use of cefuroxime.</td>
</tr>
</tbody>
</table>

| **Length of pre-intervention:** 24 months prior | The reduction in total antibiotic consumption was sustainable and did not increase over the next 36 months. |
| **Length of post-intervention:** 36 months following | |

**ITS Protection against secular changes (high quality)**

**Protection against detection bias (acceptable quality)**
<table>
<thead>
<tr>
<th><strong>Objective and participants</strong></th>
<th><strong>MDR Gram-negative bacteria</strong></th>
<th><strong>Intervention, control and follow-up</strong></th>
<th><strong>Results</strong></th>
<th><strong>Quality assessment</strong></th>
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</thead>
<tbody>
<tr>
<td>Only samples taken in the ICU were considered</td>
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<tr>
<td>Exclusion criteria: copy strains – defined as an isolate of the same species showing the same susceptibility pattern throughout a 1-month period in the same patient, no matter what the site of isolation</td>
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<tr>
<td><strong>Yong 2010</strong></td>
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<tr>
<td><strong>Setting</strong></td>
<td>Tertiary (one ICU)</td>
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<tr>
<td><strong>Australia</strong></td>
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<tr>
<td><strong>January 2000 – December 2006</strong></td>
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<tr>
<td>To perform an evaluation of changes in antibiotic susceptibility patterns in common Gram-negative organisms isolated from an ICU to demonstrate whether an observed reduction in broad-spectrum antibiotic use alters the resistance patterns of local bacteria</td>
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<tr>
<td><strong>Participants</strong></td>
<td>N=13,295</td>
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</tr>
<tr>
<td>Age: not reported</td>
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<tr>
<td>Male: not reported, female: not reported</td>
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<tr>
<td>Inclusion criteria: not reported</td>
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<tr>
<td>Exclusion criteria: not reported</td>
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<tr>
<td><strong>Bacteria:</strong> E. coli, Klebsiella spp., Enterobacter spp., P. aeruginosa, Acinetobacter spp.</td>
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<tr>
<td><strong>Resistant to:</strong></td>
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<tr>
<td>aminoglycosides, carbapenems (imipenem), cephalosporins (ceftazidime), fluoroquinolones (ciprofloxacin)</td>
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<tr>
<td><strong>Mechanism of resistance:</strong> not reported</td>
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<tr>
<td><strong>Intervention</strong></td>
<td>National guidelines on antimicrobial prescribing; antibiotic stewardship via computerized decision support systems. In 2001, one system guiding antibiotic use outside the ICU – a web-based antimicrobial approval system for third-generation cephalosporins (cefotaxime and ceftriaxone). In 2002, targeting the ICU specifically – computerized decision support system for antibiotic prescribing</td>
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<tr>
<td><strong>Length of pre-intervention:</strong> 30 months</td>
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<tr>
<td><strong>Length of post-intervention:</strong> 54 months</td>
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<tr>
<td><strong>Antibiotic use</strong></td>
<td>Following the implementation of national guidelines on antimicrobial prescribing and antibiotic stewardship, there was a significant reduction in the number of imipenem-resistant E. coli and Klebsiella spp. isolates observed in the ICU. A small but significant improvement in the number of imipenem-resistant Acinetobacter spp. isolates was also observed.</td>
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<tr>
<td>For Enterobacteriaceae with potentially inducible beta-lactamases, no significant changes was observed in imipenem susceptibility, although gentamicin susceptibility increased at a rate of 2.1%/year (95% CI 0.7–3.4), and ciprofloxacin susceptibility increased at a rate of 0.9%/year (95% CI 0.1–1.7)</td>
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<tr>
<td><strong>ITS Protection against secular changes (high quality)</strong></td>
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<tr>
<td><strong>Protection against detection bias (acceptable to low quality)</strong></td>
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<tr>
<td><strong>ICU antibiotic consumption</strong></td>
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<tr>
<td>Objective and participants</td>
<td>MDR Gram-negative bacteria</td>
<td>Intervention, control and follow-up</td>
<td>Results</td>
<td>Quality assessment</td>
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<tr>
<td>To determine the relation of carbapenem restriction with the incidence of MDR <em>A. baumannii</em> in VAP</td>
<td><em>Bacteria:</em> <em>A. baumannii</em></td>
<td><em>Intervention</em></td>
<td>The use of antibiotics to cover Gram-negative bacteria in the ICU, including third- and fourth-generation cephalosporins, carbapenems, extended-spectrum penicillins, aminoglycosides and fluoroquinolones remained stable during the study period</td>
<td><em>Quality assessment</em></td>
</tr>
<tr>
<td>Participants</td>
<td><em>Resistant to:</em> carbapenems</td>
<td><em>Control group</em></td>
<td></td>
<td>Low methodological quality (0)</td>
</tr>
<tr>
<td>19–45 years, middle aged</td>
<td><em>Mechanism of resistance:</em> ESBL</td>
<td>Conventional treatment: no restrictions of carbapenem (doctors were able to prescribe if necessary). <em>N=15</em></td>
<td>Mortality rates did not differ significantly between the treatment groups (RR 0.78; 95% CI 0.29–2.12).</td>
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<tr>
<td>Adults 46–64 years, aged 65–79 years</td>
<td></td>
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<td>Antibiotic resistance</td>
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<tr>
<td>Male: 15, female: 11</td>
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<td>More patients in the conventional group developed a carbapenem-resistant strain of <em>A. baumannii</em>, although the difference was not statistically significant (RR 0.63; 95% CI 0.38–1.04)</td>
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</tbody>
</table>

**K. pneumoniae, Klebsiella pneumonia; P. aeruginosa, Pseudomonas aeruginosa; A. baumannii, Acinetobacter baumannii; E. coli, Escherichia coli; E. aerogenes; Enterobacter aerogenes; E. cloacae, Enterobacter cloacae; S. maltophilia, Stenotrophomonas maltophilia; CRKP, carbapenem-resistant K. pneumoniae; SICU, surgical intensive care unit; TICU, trauma intensive care unit; VAP, ventilator-associated pneumonia; MDR, multi-drug resistant; ESBL, extended-spectrum beta-lactamase; BLIC, beta-lactam/beta-lactamase inhibitor combinations; ITS, interrupted time series; RCT, randomized controlled trial; ICU, intensive care unit; FQ, fluoroquinolones; 3/4CEPH, third- and fourth-generation cephalosporins; HAI, healthcare-associated infection; CI, confidence interval; RR, risk ratio; DDD, defined daily dose; SD, standard deviation.**
### 4.3.2. Other infection control measures

<table>
<thead>
<tr>
<th>Study details</th>
<th>Objective and participants</th>
<th>MDR Gram-negative bacteria</th>
<th>Intervention, control and follow-up</th>
<th>Results</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levin 2010</td>
<td>To analyse whether single patient rooms in the ICU decreased bacterial transmission between ICU patients</td>
<td><strong>Bacteria:</strong> <em>Acinetobacter</em> spp., other Gram-negative bacteria</td>
<td><strong>Intervention</strong> ICU A converted to single patient rooms. Old ICU A <em>N</em>=64, new ICU A <em>N</em>=62</td>
<td><strong>Infection control</strong> The single-room ICU A had a significantly lower ICU acquisition of resistant organisms when compared with ICU B during the same period [3/62 (5%) vs 7/39 (18%), respectively, <em>P</em>=0.043], which was confirmed using survival analysis (<em>P</em>=0.011). ICU B showed no changes over the study.</td>
<td>CBA Low methodological quality (0)</td>
</tr>
<tr>
<td></td>
<td><strong>Participants</strong> <em>N</em>=207</td>
<td><strong>Resistant to:</strong> carbapenems</td>
<td><strong>Control group</strong> ICU B remained open plan. Old ICU B <em>N</em>=44, new ICU B <em>N</em>=39</td>
<td></td>
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<tr>
<td>Setting</td>
<td>Age: not reported</td>
<td><strong>Mechanism of resistance:</strong> ESBL</td>
<td><strong>Length of follow-up:</strong> not reported</td>
<td></td>
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</tr>
<tr>
<td>Tertiary (two ICUs) Israel</td>
<td>Male: not reported, female: not reported</td>
<td></td>
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<tr>
<td>Dates not reported</td>
<td>Inclusion criteria: not reported</td>
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<tr>
<td></td>
<td>Exclusion criteria: not reported</td>
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ICU, intensive care unit; ESBL, extended-spectrum beta-lactamase; CBA, controlled before–after study.

### 4.3.3. Selective decontamination

<table>
<thead>
<tr>
<th>Study details</th>
<th>Objective and participants</th>
<th>MDR Gram-negative bacteria</th>
<th>Intervention, control and follow-up</th>
<th>Results</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agusti 2002</td>
<td>To determine the efficacy of SDD in patients with multi-drug-resistant <em>A. baumannii</em> intestinal colonization</td>
<td><strong>Bacteria:</strong> <em>A. baumannii</em></td>
<td><strong>Intervention</strong> SDD: a combination of polymyxin E (colistin) (150 mg) and tobramycine (80 mg) administered in 20-mL liquid form x 4/day (orally or through</td>
<td><strong>Bacterial colonization</strong> Rates of faecal, pharyngeal and axillary colonization did not significantly reduce during ICU stay in the control group (<em>P</em> value not reported). In the SDD group, the rate</td>
<td>Quasi-randomized Low methodological quality (0)</td>
</tr>
<tr>
<td>Quasi-randomized</td>
<td><strong>Participants</strong> <em>N</em>=54</td>
<td><strong>Resistant to:</strong> aminoglycosides (tobramycine)</td>
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<tr>
<td>Setting</td>
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</table>

<p>| CBA Low methodological quality (0) |</p>
<table>
<thead>
<tr>
<th>Study details</th>
<th>Objective and participants</th>
<th>MDR Gram-negative bacteria</th>
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<th>Results</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Tertiary (one ICU), Spain October 1998–June 1999</em></td>
<td>Adults 19–45 years, middle aged 46–64 years, aged 65–79 years Male: 16, female: 5</td>
<td>Mechanism of resistance: not reported</td>
<td>nasogastric tube), and 0.5 g of gel containing 2% of colistin and tobramycin applied round the gum margins and oropharynx x 4/day. Duration of treatment from detection of <em>A. baumannii</em> to discharge from ICU. N=21</td>
<td>of faecal and pharyngeal carriage was reduced significantly (<em>P</em>&lt;0.001 and <em>P</em>=0.003, respectively), but not the rate of cutaneous carriage</td>
<td>Small sample size</td>
</tr>
<tr>
<td><em>Mechanism of resistance: ESBL</em></td>
<td>Inclusion criteria: Intervention group 1. All patients with <em>A. baumannii</em> fecal colonization 2. An expected ICU stay exceeding five days</td>
<td><strong>Control group</strong></td>
<td>No intervention. N=33</td>
<td><strong>Length of follow-up:</strong> duration of treatment</td>
<td></td>
</tr>
<tr>
<td><em>Exclusion criteria: not reported</em></td>
<td>Control group 1. All patients admitted 1 October–30 November 1998 with <em>A. baumannii</em> faecal colonization 2. At least one series of axillary-pharyngeal-rectal swab performed</td>
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<tr>
<td><em>Brun-Buisson 1989</em></td>
<td>To study the efficacy of intestinal decontamination by oral non-absorbable antibiotic agents to control a nosocomial outbreak of intestinal colonization and infection with MDR Enterobacteriaceae, and to examine its effects on endemic nosocomial infection rates.</td>
<td><strong>Bacteria:</strong> <em>Enterobacter spp.</em>, <em>P. aeruginosa</em> <strong>Resistant to:</strong> aminoglycosides (amikacin), third-generation cephalosporins <strong>Mechanism of resistance:</strong> ESBL</td>
<td><strong>Intervention</strong></td>
<td><strong>Mortality</strong></td>
<td>Quasi-randomized</td>
</tr>
<tr>
<td><em>Quasi-randomized</em></td>
<td><strong>Participants</strong> N=86 Adults 19–45 years, middle aged 46–64 years, aged 65–79 years Male: not reported, female: not reported</td>
<td></td>
<td>SDD: a combination of polymyxin E (colistin), 50 mg; neomycin, 1 g; and nalidixic acid (quinolone), 1 g administered in liquid form x 4/day either orally or through a nasogastric tube, starting within 24 h of admission and continuing until discharge from the unit. N=36</td>
<td>All-cause mortality and mortality from nosocomial infections did not differ significantly between patients receiving SDD or no prophylaxis</td>
<td>Low methodological quality (0)</td>
</tr>
<tr>
<td><em>Setting</em> Tertiary (one ICU) France January 1987–May 1987</td>
<td></td>
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<td><strong>Control group</strong> No prophylaxis. N=50</td>
<td><strong>Clinical success/improvement</strong></td>
<td></td>
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<tr>
<td><em>Participants</em></td>
<td></td>
<td></td>
<td><strong>Length of follow-up:</strong> not reported</td>
<td><strong>There was no significant difference between patients receiving SDD or no prophylaxis in:</strong></td>
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<td></td>
<td></td>
<td></td>
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<td>– the incidence of any nosocomial infection</td>
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<td></td>
<td>– the infections caused by Gram-negative bacteria</td>
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</table>
### Study details

**Objective and participants**

Inclusion criteria:
1. Consecutive patients with unit stay exceeding two days
2. Severity score at admission >2

Exclusion criteria:
1. Severe neutropenia routinely receiving oral antibiotic prophylaxis

**MDR Gram-negative bacteria**

**Intervention, control and follow-up**

Results

Quality assessment

#### Inclusion criteria:

1. Consecutive patients with unit stay exceeding two days
2. Severity score at admission >2

#### Exclusion criteria:

1. Severe neutropenia routinely receiving oral antibiotic prophylaxis

#### Results

- the number of nosocomial infections that needed antibiotic treatment
  - There was no significant difference in the number of patients staying on ICU longer than seven or 15 days

#### Bacterial colonization

One SDD patient and 12 no prophylaxis patients were positive for MDR strains (RR 0.12; 95% CI 0.02–0.85). No new cases of MDR strains of Enterobacteriacae were detected during the first four months after the trial

#### Adverse events

Three no prophylaxis patients needed therapy for a septic episode caused by Enterobacteriacae; however, this was not significantly different from the intervention group

### Study

**Saidel-Odes 2012**

**RCT**

**Setting**

Tertiary (one internal medicine ward)

Israel

**Participants**

- **N=40**
  - Middle aged 46–64 years, aged 65–79 years
  - Male: 26, female: 14

**Inclusion criteria:**

1. Hospitalized patients with CRKP colonization with or without infection

**Bacteria:** *K. pneumoniae*

**Resistant to:** carbapenems

**Mechanism of resistance:** not reported

**Intervention**

SDD: topical application in the oropharynx of colistin sulfomethate sodium 100,000 U per g and gentamicin sulfate 1.6 mg per g incorporated into the gel. Dose of 0.5 g x 4/day for seven days. Plus an oral solution of 80 mg of gentamicin and 1x10 U of polymyxin E (colistin), given orally or through a nasogastric tube x 4/day for seven days.

**N=20**

**Mortality**

The rate of mortality did not differ significantly between the SDD group and the placebo group. The causes of mortality were not reported. No adverse events were reported

**Antibiotic susceptibility**

CRKP isolates from patients in the SDD arm remained susceptible to gentamicin and polymyxin E throughout the study (MIC ≤2 mg/mL and ≤0.094 mg/mL, respectively)

**Quality assessment**

**RCT**

High methodological quality (+++)

Small sample size
<table>
<thead>
<tr>
<th>Study details</th>
<th>Objective and participants</th>
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</tr>
</thead>
</table>
| November 2008–June 2010 | 2. >18 years of age  
3. Available for a follow-up period (while hospitalized or as outpatients) of at least seven weeks  
Exclusion criteria: <18 years of age, pregnancy, lactation, a known allergy to one of the study drugs, renal failure with creatinine clearance less than 50 mL/min, treatment with intravenous gentamicin or intravenous polymyxin E at the time of randomization | | **Control group**  
Placebo: topical application in the oropharynx of the placebo gel, which was compounded from carboxymethyl cellulose. Dose of 0.5 g x 4/day for seven days. Plus two oral solutions, one containing sodium chloride 0.45% and the other containing pulverized sacarin, given orally or through a nasogastric tube X 4/day for seven days. N=20 | **Bacterial colonization**  
At the end of treatment, the number of participants in the SDD group that had a throat culture that was CRKP positive reduced from 30% to 0%, whereas in the placebo group, this reduced from 35% to 30% (P<0.0001) | |

*A. baumannii, Acinetobacter baumannii; K. pneumoniae, Klebsiella pneumoniae; MDR, multi-drug resistant; SDD, selective digestive decontamination; RR, risk ratio, CI, confidence interval; CRKP, carbapenem-resistant K. pneumonia; MIC, minimum inhibitory concentration; RCT, randomized controlled trial; ICU, intensive care unit.*
### 4.3.4. Systematic reviews

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<th>Study details</th>
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<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Falagas 2009</strong>&lt;sup&gt;*&lt;/sup&gt;</td>
<td>To assess the clinical and microbiological effectiveness of fosfomycin in the treatment of MDR, XDR or PDR non-fermenting Gram-negative bacterial infections</td>
<td><strong>Bacteria:</strong> <em>Pseudomonas</em> spp., <em>Acinetobacter</em> spp., <em>Stenotrophomonas</em> spp. and <em>Burkholderia</em> spp.</td>
<td><strong>Intervention</strong> Fosfomycin</td>
<td><strong>Microbiological:</strong> a total of 1859 MDR non-fermenting Gram-negative isolates. Susceptibility rate to fosfomycin of MDR <em>P. aeruginosa</em> isolates was ≥90% and 50–90% in 7/19 and 4/19 relevant studies, respectively. 30.2% isolates of MDR <em>P. aeruginosa</em>, 3.5% MDR <em>A. baumannii</em> isolates were found to be susceptible to fosfomycin</td>
<td>Low methodological quality (0)</td>
</tr>
<tr>
<td><strong>Setting</strong> International</td>
<td><strong>Participants</strong> N=33 Studies: 23 microbiological, one animal and three cohort studies and three case reports Inclusion criteria: microbiological, animal experimental or clinical data on the effect of fosfomycin against MDR non-fermenting Gram-negative pathogens such as <em>Pseudomonas</em> spp., <em>Acinetobacter</em> spp., <em>Stenotrophomonas</em> spp. and <em>Burkholderia</em> spp. MDR, XDR or PDR non-fermenting Gram-negative bacilli or to Gram-negative bacilli with resistance to two or more classes of potentially effective antimicrobial agents Exclusion criteria: studies written in languages other than English, French, German, Italian or Spanish.</td>
<td>See Table II in the paper for details of clinical studies</td>
<td><strong>Control group</strong> Combination of fosfomycin with other antimicrobial agents</td>
<td><strong>Clinical:</strong> 91% of the patients clinically improved (treatment of infections caused by MDR <em>P. aeruginosa</em>)</td>
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</tr>
<tr>
<td><strong>Search up to January 2009</strong></td>
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<td>This review was included because it is on the topic; however, the conclusions reached are not supported by the study design</td>
</tr>
</tbody>
</table>
To evaluate the available clinical evidence regarding the effectiveness and safety of systemic colistin in children without cystic fibrosis.

**Participants**

- Studies: 10 case series and 15 case reports
- Inclusion criteria: studies with data regarding the use of intravenous, intrathecal, intramuscular or intraventricular colistin in paediatric patients for the treatment of infections caused by colistin-susceptible pathogens or for prophylaxis. All or the majority of patients involved in each individual study should not have cystic fibrosis.
- Exclusion criteria: studies that focused on colistin use in paediatric patients with cystic fibrosis, or reporting the use of oral colistin or the use of colistin for topical treatment in paediatric patients. Abstracts in scientific conferences or studies published in languages other than English, Spanish, French, German, Italian or Greek.

**Bacteria**: P. aeruginosa, A. baumannii, K. aerogenes, H. influenza, P. pyocyain, P. aeruginosa, K. pneumoniae and A. aerogenes

See Table I in the paper for details of studies.

**Intervention**

Colistin for the treatment of infections (N=326)

**Control group**

Colistin for surgical prophylaxis or prophylaxis of infections in burns patients (N=44)

**Case series treatment:**

- 271 evaluable subjects
- Cure: 235/271
- Improvement: 10/271
- Deterioration: 6/271
- Death: 20/271

Adverse effects (included in safety assessment N=311)

1. Nephrotoxicity: 33/311 had cylindruria or haematuria, 8/311 had a blood urea nitrogen elevation of >10% (in one child owing to an overdosage of colistin), 5/311 had renal tubular cells in the urine, 3/311 had proteinuria and 2/311 had a significant increase in serum creatinine levels during intravenous colistin treatment. Data regarding adverse events not provided for two children.
2. Neurotoxicity: 0/311
3. Other: 8/311

**Case series prophylaxis:**

- Incidence of infection: 0/44
- Death: 9/44 attributed to the underlying pathologies. No signs of colistin-related toxicity were found.

Adverse effects:

1. Tubular epithelial cells in urine, persistent for up to 31 days.

This review was included because it is on the topic; however, the conclusions reached are not supported by the study design.
<table>
<thead>
<tr>
<th>Study details</th>
<th>Objective and participants</th>
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<th>Intervention, control and follow-up</th>
<th>Results</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falagas 2010³ Setting International Searches up to January 2009</td>
<td>To the evidence on fosfomycin as a treatment option for infections caused by members of the family Enterobacteriaceae with advanced resistance to antimicrobial drugs, including producers of ESBL</td>
<td>Bacteria: Microbiological studies <em>K. pneumoniae</em> isolates, <em>E. coli</em> Clinical studies <em>E. coli</em>, <em>S. typhimurium</em>, <em>S. typhi</em> See Table III in the paper for details of studies</td>
<td>Intervention Amoxicillin-clavulanate potassium Control group Fosfomycin–trometamol in two of the <em>E. coli</em> studies</td>
<td>Microbiological success 11 of the 17 studies reported that at least 90% of the isolates were susceptible to fosfomycin Clinical efficacy Measured in four studies. Two studies oral treatment for lower UTI with ESBL-producing <em>E. coli</em> (one prospective and one retrospective) resulted in the treatment group with clinical cure in 75 of the 80 (93.8%) patients included in these studies. Two case reports of infection due to MDR <em>Salmonella</em> spp. Reported treatment was effective with fosfomycin</td>
<td>Low methodological quality (0) This review was included because it is on the topic; however, the conclusions reached are not supported by the study design.</td>
</tr>
<tr>
<td>Study details</td>
<td>Objective and participants</td>
<td>MDR Gram-negative bacteria</td>
<td>Intervention, control and follow-up</td>
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<tr>
<td>Falagas 2012*</td>
<td>To identify and evaluate the available data regarding the susceptibility of recent Gram-negative bacteria to isepamicin, including that of MDR strains of bacteria</td>
<td>Bacteria: Clinical studies S. epidermidis, E. coli, S. pneumoniae, P. aeruginosa</td>
<td>Intervention Isepamicin</td>
<td>Microbiological: isepamicin was more effective in four studies than amikacin, six studies reported as effective, one study both groups ineffective. In studies including MDR bacteria, 2/4 reported more effective than amikacin; 1/4 as effective as amikacin; 1/4 both isepamicin and amikacin ineffective</td>
<td>Low methodological quality (0)</td>
</tr>
<tr>
<td>Setting Not reported</td>
<td>Participants N=512 Studies=11 microbiological, one RCT, one prospective study, one retrospective study</td>
<td>See Table II in the paper for details of studies</td>
<td>Control group Two clinical studies – amikacin one clinical study – isepamicin + levofloxacin for prophylaxis</td>
<td>Clinical: 1. Paediatric infection treatment studies: 100% clinical and bacteriological response for both the isepamicin and the amikacin arms. Definition of clinical response not stated (e.g. cure, improvement) 2. Prophylactic study: acute bacterial prostatitis 1.3%</td>
<td></td>
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<tr>
<td>Searches from 2000 to 2010</td>
<td>Exclusion criteria: either a microbiological (in-vitro) study that evaluated the susceptibility of Gram-negative bacterial isolates (including MDR ones) to isepamicin or a clinical study that evaluated the use of isepamicin, given for the treatment of infections by the aforementioned pathogens or for prophylaxis for this type of infection. In addition, studies deemed relevant should have been published between 2000 and 2010</td>
<td>Exclusion criteria: studies that examined a sample of fewer than 10</td>
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<td></td>
<td>Exclusion criteria: abstracts in scientific conferences or studies published in languages other than English, Spanish, French, German, Italian or Greek</td>
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<td>This review was included because it is on the topic; however, the conclusions reached are not supported by the study design</td>
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<td>Study details</td>
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<td>Results</td>
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<tr>
<td>Study details</td>
<td>isolates or patients, studies referring to synergistic or pharmacodynamic/pharmacokinetic parameters of isepamicin, studies that provided data regarding the susceptibility of isepamicin to micro-organisms other than Gram-negative bacteria or the susceptibility of other aminoglycosides only to Gram-negative bacteria. Abstracts in scientific conferences or studies published in languages other than English, Spanish, French, German or Italian</td>
<td>Bacteria: P. aeruginosa, A. baumannii, E. coli, Klebsiella spp., ESBL</td>
<td>Intervention: Antimicrobial stewardship: 1. Antibiotic restriction/pre-approval 2. Computer-assisted decision support 3. Infectious diseases consultant 4. Re-assessment on pre-specified date 5. Antibiotic de-escalation protocols 6. Antibiotic prophylaxis guideline 7. Antibiotic treatment guideline</td>
<td>Overall stewardship intervention: 1. Reductions in antimicrobial utilization (11–38% defined daily dose/1000 patient-days) 2. Lower total antimicrobial costs (US$ 5–10/patient-day) 3. Shorter average duration of antibiotic therapy 4. Less inappropriate use 5. Fewer antibiotic adverse events. stewardship intervention beyond six months: 1. Reductions in antimicrobial resistance rates</td>
<td>High methodological quality (++)</td>
</tr>
<tr>
<td>Kaki 2011s</td>
<td>To evaluate the current state of evidence for antimicrobial stewardship interventions in the critical care unit</td>
<td>Control group: Not reported, presumably no stewardship</td>
<td></td>
<td>Antibiotic stewardship was not associated with increases in nosocomial infection rates, length of stay or mortality</td>
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<tr>
<td>Setting</td>
<td>Internation</td>
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<tr>
<td>Search</td>
<td>January 1996 to December 2010</td>
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<tr>
<td>Participants</td>
<td>N=not available/not reported for all included studies Studies: three RCTs, three ITSs, and 18 uncontrolled before–after studies Inclusion criteria: application of any intervention; to improve antimicrobial utilization; and within an intensive care setting Exclusion criteria: if no intervention was applied, non-human or non-patient based, non-hospital based, or they did not involve intensive care</td>
<td>See Table I in the paper for details of studies.</td>
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<td>Study details</td>
<td>Objective and participants</td>
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<td>Intervention, control and follow-up</td>
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<tr>
<td>Siempos 2007&lt;sup&gt;6&lt;/sup&gt;</td>
<td>To clarify whether carbapenems are more effective or safer than other broad-spectrum antibiotics for the empirical treatment of patients with HAP</td>
<td><strong>Bacteria:</strong> P. aeruginosa&lt;br&gt;See Table I in the paper for details of studies</td>
<td><strong>Intervention</strong>&lt;br&gt;Carbapenems:&lt;br&gt;1. Imipenem/ cilastatin (eight studies)&lt;br&gt;2. Meropenem (four studies)&lt;br&gt;<strong>Control group</strong>&lt;br&gt;Imipenem/ cilastatin compared with:&lt;br&gt;1. Fluoroquinolones: levofloxacin, ciprofloxacin (three studies)&lt;br&gt;2. Other beta-lactams: piperacillin/tazobactam, aztreonam, cefepime, ceftazidime (five studies)&lt;br&gt;Meropenem compared with:&lt;br&gt;combination of a cephalosporin (ceftazidime, cefuroxime) with an aminoglycoside (amikacin, gentamicin, tobramycin)</td>
<td>1. All-cause mortality: lower mortality in the carbapenems group (OR 0.72, 95% CI 0.55–0.95)&lt;br&gt;2. Treatment success (clinical): no difference between groups (OR 1.08, 95% CI 0.91–1.29)&lt;br&gt;3. Treatment success (microbiological): no difference between groups (OR 1.04, 95% CI 0.72–1.50)&lt;br&gt;4. Adverse effects: no difference (0.81, 0.46–1.43)&lt;br&gt;P. aeruginosa pneumonia subgroup: lower treatment success (OR 0.42, 95% CI 0.22–0.82) and lower eradication of Pseudomonas spp. strains (OR 0.50, 95% CI 0.24–0.89) in the carbapenems group.&lt;br&gt;Lat onset of HAP subgroup: no difference between groups (OR 1.34, 95% CI 0.91–1.97)</td>
<td>High methodological quality (++)</td>
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<td>Setting</td>
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<td>Search</td>
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<td>January 1950 to March 2006</td>
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<td>Study details</td>
<td>Objective and participants</td>
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<td>haematological malignancies and trials that included fewer than 10 patients with pneumonia who received a carbapenem. Experimental trials and trials focusing on pharmacokinetic and pharmacodynamics parameters. Finally, RCTs comparing the effectiveness and safety of two different carbapenems</td>
<td>P. aeruginosa, Pseudomonas aeruginosa; A. baumannii, Acinetobacter baumannii; K. aerogenes, Klebsiella aerogenes; H. influenza, Haemophilus influenza; P. pyocyana, Pseudomonas pyocyana; K. pneumoniae, Klebsiella pneumoniae; A. aerogenes, Aerobacter aerogenes; E. coli; Escherichia coli; S. typhimurium, Salmonella typhimurium; S. typhi, Salmonella typhi; S. pneumoniae, Streptococcus pneumoniae; S. epidermis, Staphylococcus epidermidis; MDR, multi-drug resistant; XDR, extensively drug resistant; PDR, pan-drug resistant; RCT, randomized controlled trial; ESBL, extended-spectrum beta-lactamase; HAP, hospital-acquired pneumonia; OR, odds ratio; CI, confidence interval.</td>
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### 4.3.5. Treatment

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<tr>
<th>Study details</th>
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<th>MDR Gram-negative bacteria</th>
<th>Intervention, control and follow-up</th>
<th>Results</th>
<th>Quality assessment</th>
</tr>
</thead>
</table>
| Betrosian 2007 | To evaluate the clinical efficacy and safety of high-dose regimen ampicillin sulbactam for the treatment of VAP from MDR *A. baumannii* | **Bacteria:** *A. baumannii*  
**Resistant to:** ampicillin/sulbactam and susceptible exclusively to colistin (polymyxin E)  
**Mechanism of resistance:** not reported | **Intervention**  
Ampicillin/sulbactam at a rate 2:1 every 8 h. 24 g/12 g daily for seven to 10 days. *N=13*  
**Control group**  
Ampicillin/sulbactam at a rate 2:1 every 8 h. 18 g/9 g daily for seven to 10 days. *N=14* | **Mortality**  
14-day VAP mortality and 30-day all-cause mortality were not significantly different between treatment groups  
**Clinical success/improvement**  
The number of patients with clinical success and clinical failure was not significantly different between treatment groups  
**Bacterial colonization**  
The two treatment groups showed no difference in the eradication of *A. baumannii* isolates (bacteriological success), bacteriological failure or superinfection  
**Adverse events**  
There was no difference in the adverse effects experienced by participants | RCT  
Low methodological quality (0) |
| Setting | | | | | |
| Tertiary (1 ICU) | | | | | Very small sample size |
| Greece | | | | | |
| October 2004–February 2006 | | | | | |
| Betrosian 2008 | To compare the clinical efficacy and safety of high-dose ampicillin/sulbactam vs colistin as monotherapy for the treatment of *Acinetobacter* spp. VAP | **Bacteria:** *A. baumannii*  
**Resistant to:** Aminoglycosides, carbapenems, | **Intervention**  
Colistin, intravenous 3 MIU every 8 h for eight to 10 days. *N=15* | **Mortality**  
14-day VAP mortality and 28-day all-cause mortality were not significantly different between treatment groups | RCT  
Low methodological quality (0) |
<p>| RCT | | | | | |</p>
<table>
<thead>
<tr>
<th>Study details</th>
<th>Objective and participants</th>
<th>MDR Gram-negative bacteria</th>
<th>Intervention, control and follow-up</th>
<th>Results</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting</td>
<td>Participants</td>
<td>cephalosporins,</td>
<td>Control group</td>
<td>Clinical success/improvement</td>
<td>Small sample size</td>
</tr>
<tr>
<td>Tertiary (2</td>
<td>N=28</td>
<td>fluoroquinolones</td>
<td>Ampicillin/sulbactam, 9 g (at a</td>
<td>The number of patients with</td>
<td></td>
</tr>
<tr>
<td>ICUs)</td>
<td>Middle aged 46–64 years,</td>
<td>Mechanism of</td>
<td>rate 2:1 every 8 h for eight to</td>
<td>clinical success and</td>
<td></td>
</tr>
<tr>
<td>Greece</td>
<td>aged 65–79 years</td>
<td>resistance: not</td>
<td>10 days, administered as follows:</td>
<td>clinical failure was</td>
<td></td>
</tr>
<tr>
<td>Dates not</td>
<td>Male: 14, female: 14</td>
<td>reported</td>
<td>three vials (20 mL each) containing</td>
<td>not significantly different</td>
<td></td>
</tr>
<tr>
<td>reported</td>
<td>Inclusion criteria:</td>
<td></td>
<td>3.0 g of ampicillin/sulbactam</td>
<td>between treatment groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ventilated patients for &gt;72</td>
<td></td>
<td>diluted in 200 mL of 5% dextrose</td>
<td>Bacterial colonization</td>
<td></td>
</tr>
<tr>
<td></td>
<td>h who developed MDR A.</td>
<td></td>
<td>provided within 1-h duration</td>
<td>The two treatment groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>baumannii VAP</td>
<td></td>
<td>infusion.</td>
<td>showed no difference in</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria:</td>
<td></td>
<td>N=13</td>
<td>the eradication of A.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cases of VAP with</td>
<td></td>
<td>Length of follow-up: two-week-</td>
<td>baumannii isolates (</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mixed isolated micro-</td>
<td></td>
<td>and one-month mortalities</td>
<td>bacteriological success)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>organisms, combination</td>
<td></td>
<td></td>
<td>or bacteriological failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>antibiotic therapy, allergy</td>
<td></td>
<td></td>
<td>(persistence of A. baumannii</td>
<td></td>
</tr>
<tr>
<td></td>
<td>to beta-lactamase or</td>
<td></td>
<td></td>
<td>isolates (&gt;104 CFU/mL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>penicillin, or previous</td>
<td></td>
<td></td>
<td>Adverse events</td>
<td></td>
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<tr>
<td></td>
<td>enrolment in similar studies</td>
<td></td>
<td></td>
<td>There was no difference in</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>the adverse effects</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>experienced by participants</td>
<td></td>
</tr>
<tr>
<td>Chastre</td>
<td>To compare the efficacy of</td>
<td>Bacteria: E. coli,</td>
<td>Intervention</td>
<td>Mortality</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>eight days vs 15 days of</td>
<td>Klebsiella spp., Enterobacter spp., P.</td>
<td>Antibiotics for eight days:</td>
<td>28-day and 60-day all-cause</td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td>antibiotic treatment of</td>
<td>aeruginosa, Acinetobacter spp., Proteus spp., Serratia spp., C. freundii, M.</td>
<td>specific antibiotics, doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting</td>
<td>patients with microbiologically prove</td>
<td></td>
<td>morgagni</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertiary (51</td>
<td>N=401</td>
<td>Bacteria: E. coli,</td>
<td>schedules are not reported.</td>
<td>mortality and in-hospital</td>
<td></td>
</tr>
<tr>
<td>ICUs)</td>
<td>Middle aged 46–64 years,</td>
<td>Klebsiella spp., Enterobacter spp., P.</td>
<td>Antibiotics were selected by the</td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>aged 65–79 years</td>
<td>aeruginosa, Acinetobacter spp., Proteus spp., Serratia spp., C. freundii, M.</td>
<td>treating physicians. As per</td>
<td></td>
<td></td>
</tr>
<tr>
<td>May 1999-</td>
<td>Male: 141, female: 46</td>
<td>morgagni</td>
<td>protocol, the initial regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>June 2002</td>
<td>Inclusion criteria:</td>
<td>Resistant to: ticarcillin,</td>
<td>should have preferably combined at</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. &gt;18 years of age</td>
<td>methicillin</td>
<td>least an aminoglycoside, or a</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Clinical suspicion of VAP</td>
<td>Mechanism of resistance:</td>
<td>fluoroquinolone and a broad-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Positive quantitative</td>
<td>ESBL</td>
<td>spectrum beta-lactam antimicrobial</td>
<td>Clinical success/improvement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cultures of distal</td>
<td>Intervention</td>
<td>agent. N=197</td>
<td>Mortality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pulmonary secretion samples</td>
<td>Intervention</td>
<td></td>
<td>28-day and 60-day all-cause</td>
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<tr>
<td></td>
<td></td>
<td>Intervention</td>
<td></td>
<td>mortality and in-hospital</td>
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<tr>
<td></td>
<td></td>
<td>antibiotics for eight</td>
<td></td>
<td>mortality did not significantly differ between the</td>
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<td></td>
<td></td>
<td>days: specific antibiotics,</td>
<td></td>
<td>eight- and 15-day regimes</td>
<td></td>
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<td></td>
<td></td>
<td>doses and schedules are</td>
<td></td>
<td>Clinical success/improvement</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>not reported.</td>
<td></td>
<td>Risk differences (90% CIs)</td>
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<td></td>
<td></td>
<td>Antibiotics were selected</td>
<td></td>
<td>to develop an unfavourable</td>
<td></td>
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<td></td>
<td></td>
<td>by the treating physicians.</td>
<td></td>
<td>outcome (defined as death,</td>
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<tr>
<td></td>
<td></td>
<td>As per protocol, the</td>
<td></td>
<td>pulmonary infection</td>
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<td></td>
<td></td>
<td>initial regimen should</td>
<td></td>
<td>recurrence, or prescription</td>
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<td></td>
<td></td>
<td>have preferably combined</td>
<td></td>
<td>of a new antibiotic for any</td>
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<tr>
<td></td>
<td></td>
<td>at least an aminoglycoside,</td>
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<td>reason provided for ≥48 h)</td>
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<tr>
<td></td>
<td></td>
<td>or a fluoroquinolone and</td>
<td></td>
<td>were not significantly</td>
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<td></td>
<td></td>
<td>a broad-spectrum beta-</td>
<td></td>
<td>different between the eight-</td>
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<td></td>
<td></td>
<td>lactam antimicrobial agent.</td>
<td></td>
<td>and 15-day regimes for all</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control group</td>
<td></td>
<td>patients (RR 2.6, 90% CI -5.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=197</td>
<td>Control group</td>
<td></td>
<td>to 10.7) and for those patients with</td>
<td></td>
</tr>
<tr>
<td>Study details</td>
<td>Objective and participants</td>
<td>MDR Gram-negative bacteria</td>
<td>Intervention, control and follow-up</td>
<td>Results</td>
<td>Quality assessment</td>
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</tr>
<tr>
<td>4. Instigation within the 24 h following of appropriate empirical antibiotic therapy directed against the micro-organism/s responsible for the infection</td>
<td></td>
<td>Antibiotics for 15 days: specific antibiotics, doses and schedules are not reported. Antibiotics were selected by the treating physicians. As per protocol, the initial regimen should have preferably combined at least an aminoglycoside or a fluoroquinolone and a broad-spectrum beta-lactam antimicrobial agent. N=204</td>
<td></td>
<td>non-fermenting Gram-negative bacteria (RR 8.6, 90% CI -5.9 to 23.1)</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td></td>
<td></td>
<td></td>
<td>The rate of and time to (Kaplan-Meier method, log-rank test) pulmonary infection considered to be recurrence, relapses or superinfection was not significantly different between treatment regimes.</td>
<td></td>
</tr>
<tr>
<td>1. Pregnant</td>
<td></td>
<td></td>
<td></td>
<td><strong>Antibiotic use</strong></td>
<td></td>
</tr>
<tr>
<td>2. Enrolled in another trial</td>
<td></td>
<td></td>
<td></td>
<td>The number of antibiotic-free days was significantly less for all patients on the eight-day regime, but not for those patients with non-fermenting Gram-negative bacteria.</td>
<td></td>
</tr>
<tr>
<td>3. Little chance of survival</td>
<td></td>
<td></td>
<td></td>
<td>No difference was found in the number of patients continuing to receive antibiotics after the end of the trial treatment regimen, or in the number of patients who received an additional course of antibiotics</td>
<td></td>
</tr>
<tr>
<td>4. Neutropenia</td>
<td></td>
<td></td>
<td></td>
<td><strong>Antibiotic resistance</strong></td>
<td></td>
</tr>
<tr>
<td>5. Concomitant acquired immunodeficiency syndrome</td>
<td></td>
<td></td>
<td></td>
<td>For patients who developed recurrent pulmonary infections, those who had received the eight-day treatment of antibiotics had significantly less emergence of MDR pathogens compared with those who had received the 15-day treatment (42.1% vs 62.3% of recurrent infections, respectively; P=0.04)</td>
<td></td>
</tr>
<tr>
<td>6. Immunosuppressants or long-term corticosteroid therapy</td>
<td></td>
<td></td>
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<tr>
<td>7. Concomitant extrapulmonary infection that required prolonged antimicrobial treatment</td>
<td></td>
<td></td>
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<tr>
<td>8. Attending physical declined full-life support.</td>
<td></td>
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<tr>
<td>9. Early-onset pneumonia (within the first five days of mechanical ventilation) and no antimicrobial therapy during the 15 days preceding infection.</td>
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</tr>
<tr>
<td>Study details</td>
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<td>Intervention, control and follow-up</td>
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<td>Quality assessment</td>
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</tr>
<tr>
<td>Cox 1987 RCT</td>
<td>To compare the efficacy of norfloxacin vs standard parenteral treatment of non-bacteraemic, hospital-acquired UTI</td>
<td>Bacteria: <em>E. coli</em>, <em>Klebsiella</em> spp., <em>Enterobacter</em> spp., <em>P. aeruginosa</em>, <em>Serratia</em> spp., <em>C. freundii</em>, <em>M. morgagnii</em></td>
<td><strong>Intervention</strong>&lt;br&gt;Norfloxacin 400 mg x2/day, minimum treatment seven days. <em>N</em>=52 (46 evaluable patients)&lt;br&gt;<strong>Control group</strong>&lt;br&gt;Aminoglycosides alone; aminoglycosides and mezlocillin/ticarcillin; aminoglycosides and cephalexin; aminoglycosides and vancomycin, cephalexin, cefotaxime alone, administered in accordance with the manufacturers' guidelines. <em>N</em>=52 (48 evaluable patients)</td>
<td><strong>Clinical success/improvement</strong>&lt;br&gt;No significant differences were found between norfloxacin and standard parenteral antibiotic treatment in the rate of participants that were clinically cured, showed clinical improvement or had treatment failure</td>
<td><strong>RCT</strong>&lt;br&gt;Acceptable methodological quality (+)</td>
</tr>
<tr>
<td>Setting Secondary (two hospitals) USA</td>
<td><strong>Participants</strong>&lt;br&gt;<em>N</em>=104&lt;br&gt;Age: not reported&lt;br&gt;Male: not reported, female: not reported</td>
<td><strong>Resistant to</strong>: not reported</td>
<td><strong>Mechanism of resistance</strong>: not reported</td>
<td><strong>Superinfection</strong>&lt;br&gt;Rates of superinfection and early re-infection also did not differ significantly between the norfloxacin and standard parenteral antibiotic treatment groups</td>
<td><strong>Antibiotic resistance</strong>&lt;br&gt;No differences in the number of patients experiencing adverse events were found between those receiving norfloxacin and those receiving standard parenteral antibiotics</td>
</tr>
<tr>
<td>Study details</td>
<td>Objective and participants</td>
<td>MDR Gram-negative bacteria</td>
<td>Intervention, control and follow-up</td>
<td>Results</td>
<td>Quality assessment</td>
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</tbody>
</table>
| Giamarello 1990 | To evaluate the efficacy of monotherapy with pefloxacin in secondary ICU pulmonary infections in comparison with imipenem | **Bacteria:** *E. coli, K. pneumoniae, Enterobacter spp.* (various Enterobacteriaceae), *P. aeruginosa, A. anitratus, P. mira, S. marcescens* | **Intervention** Pefloxacin intravenously 400 mg, every 8 h for 11.5 (SD 5.8) days. *N=35*  
**Control group** Imipenem intravenously 1 g every 8 h for 12.9 (SD 6.2) days. *N=36*  
**Length of follow-up:** duration of treatment | **Mortality** There were three deaths related to sepsis in the imipenem group and one in the pefloxacin group (although the sepsis was not related to the bronchopneumonia, but to an underlying abdominal infection). All-cause mortality was not reported | **RCT** Acceptable methodological quality (+) |
| Huttner 2013 | To investigate if intestinal carriage of ESBL-E can be eradicated | **Bacteria:** *Enterobacter* spp. (ESBL-E) | **Intervention** Colistin sulfate 50 mg (equivalent to 42 mg colistin) | **Clinical success/improvement** The rate of eradication of ESBL-E was significantly different between | **RCT** |
### Study details

**Objective and participants**  

**MDR Gram-negative bacteria**  

**Intervention, control and follow-up**  

**Results**  

**Quality assessment**

<table>
<thead>
<tr>
<th>Study details</th>
<th>Objective and participants</th>
<th>MDR Gram-negative bacteria</th>
<th>Intervention, control and follow-up</th>
<th>Results</th>
<th>Quality assessment</th>
</tr>
</thead>
</table>
| RCT Setting  | Participants  
Adolescents 13–18 years, adults  
19–45 years, middle aged 46–64  
years, aged 65–79 years, elderly  
80+ years  
Male: 34, female: 24  
Inclusion criteria: aged ≥18 years;  
ESLB-E-positive rectal swab  
Exclusion criteria: patients with  
active ESLB infection, patients  
treated with antibiotics active against  
ESLB-E, pregnancy/breastfeeding,  
contraindication to the use of study  
drugs, previous study enrolment and  
resistance of the colonizing ESLB-E  
strain to colistin (defined as MIC >2  
mg/L)  | Resistant to:  
cefotaxime, cefotaxime/  
clavulanic acid,  
ceftazidime,  
ceftazidime/clavulanic  
acid, cefepime,  
cefepime/clavulanic  
acid  
Mechanism of  
resistance: ESBL  | base or 1.26 million units 4x/day)  
and neomycin sulfate (250 mg  
equivalent to 178 mg neomycin  
basis 4x/day) for 10 days.  
In the presence of ESBL-E  
bacteriuria, the patients were  
also treated with nitrofurantoin  
(100 mg 3x/day) for five days.  
N=27  | treatment regimes during treatment  
(day 6; RR 0.40; 95% CI 0.23–0.70)  
or in the first day after treatment (RR  
0.42; 95% CI 0.23–0.76), but did not  
differ in the end of follow-up  
**Treatment adherence**  
There was no significant difference  
between groups in the number of  
patients that adhered to treatment,  
measured by counting the number of  
pills on the boxes of study  
medication  
**Adverse events**  
No statistically significant difference  
was found  
between the treatment  
groups in the number of patients with  
at least one episode of liquid stool  | High methodological  
quality (+++)  |
| Moskowitz  
2011 | To assess whether biofilm-growing  
bacteria susceptibility testing of *P.  
aeruginosa* correlates better with  
clinical outcomes in chronic cystic  
fibrosis airway infections, when  
compared with conventional  
antibiotic susceptibility testing  
Participants  
N=39  
Adolescents 13–18 years, adults  
19–45 years  
Male: 25, female: 14  | Bacteria: *P. aeruginosa*  
Resistant to:  
aminglycosides,  
fluoroquinolones  
Mechanism of  
resistance: not reported  | Intervention  
Biofilm testing: biofilm regimens  
of two antibiotics were selected  
centrally using a published  
algorithm, which calculated for  
each bacterial morphotype the  
biofilm minimum inhibitory  
quotient of each drug, defined as  
achievable serum concentration  
divided by biofilm MIC.  
N=20  | Antibiotic susceptibility  
Participants were assigned to 12  
different regimens. The most  
common regimens included  
meropenem (52%) and ciprofloxacin  
(49%). Azithromycin-containing  
regimens were used for only two  
participants (5%), both in the biofilm  
group. No participant received  
ceftazidime and tobramycin, a  
combination commonly used in  
cystic fibrosis clinical practice  | RCT  
Acceptable  
methodological  
quality (+)  
Small sample  
size |
<table>
<thead>
<tr>
<th>Study details</th>
<th>Objective and participants</th>
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<th>Intervention, control and follow-up</th>
<th>Results</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>October 2007</td>
<td>Inclusion criteria: diagnosis of cystic fibrosis, history of persistent <em>P. aeruginosa</em> airway infection, clinical stability at the time of screening, ≥14 years with at least one prior course of intravenous antibiotics</td>
<td><em>Intervention</em> antibiotics were selected centrally using a published algorithm, which calculated for each bacterial morphotype the conventional minimum inhibitory quotient of each drug defined as achievable serum concentration divided by conventional MIC. <em>N</em>=19</td>
<td>Of the agents tested, meropenem was most active against biofilm-grown bacteria, but antibiotic regimens based on biofilm testing did not differ significantly from regimens based on conventional testing in terms of microbiological and clinical responses</td>
<td>RCT Acceptable methodological quality (+)</td>
<td></td>
</tr>
<tr>
<td><strong>Rattanaumpawan 2010</strong></td>
<td><strong>RCT</strong></td>
<td><strong>Setting</strong></td>
<td><strong>Tertiary (one hospital)</strong></td>
<td><strong>Thailand</strong></td>
<td><strong>July 2006–September 2009</strong></td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>To determine whether nebulized CMS as adjunctive therapy of Gram-negative VAP was safe and beneficial</td>
<td><strong>Bacteria:</strong> <em>E. coli</em> (ESBL +ve) and <em>E. coli</em> (ESBL -ve), <em>K. pneumoniae</em> (ESBL +ve) and <em>K. pneumoniae</em> (ESBL -ve), <em>E. cloacae</em>, <em>P. aeruginosa</em>, <em>A. baumannii</em></td>
<td><strong>Intervention</strong> Systemic antibiotic and nebulized CMS (parenteral) equivalent to 75 mg of colistin base reconstituted in 4 mL of NSS every 12 h via a nebulizer for 10 min. Continued until systemic antibiotic therapy of VAP was ended (decided by physician). <em>N</em>=51</td>
<td><strong>Mortality</strong> Rates of mortality due to VAP and all-cause mortality did not differ between the groups receiving intervention or control</td>
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</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>Hospitalized patients, ≥18 years of age, diagnosis of Gram-negative VAP</td>
<td><strong>Resistant to:</strong> aminoglycosides, carbapenems, fluoroquinolones</td>
<td><strong>Clinical success/improvement</strong> Favourable microbiological outcome was significantly higher in the intervention group compared with the control group (RR 1.57, 95% CI 1.03–2.37), but no significant difference was observed on clinical outcomes</td>
<td></td>
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</tr>
<tr>
<td><strong>Exclusion criteria</strong></td>
<td>Not reported</td>
<td><strong>Mechanism of resistance:</strong> ESBL</td>
<td><strong>Control group</strong> Systemic antibiotic(s) plus NSS equivalent to 75 mg of colistin base reconstituted in 4 mL of NSS every 12 h via a nebulizer for 10 min. Continued until systemic antibiotic therapy of VAP was ended. <em>N</em>=49</td>
<td>The overall incidence of complications, bronchospasm and renal impairment did not differ between the two treatment groups</td>
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</tr>
<tr>
<td>Study details</td>
<td>Objective and participants</td>
<td>MDR Gram-negative bacteria</td>
<td>Intervention, control and follow-up</td>
<td>Results</td>
<td>Quality assessment</td>
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<td><strong>Stenderup 1983</strong>&lt;br&gt;RCT&lt;br&gt;Setting: Community&lt;br&gt;Denmark&lt;br&gt;Dates not reported</td>
<td>To study the use of mecillinam as a prophylactic for travellers' diarrhoea</td>
<td>Bacteria: <em>Enterotoxogeni E. coli</em>&lt;br&gt;Resistant to: mecillinam, tetracycline, sulfonamide, streptomycin, chloramphenicol, kanamycin, ampicillin, cephalosporin, carbenicillin&lt;br&gt;Mechanism of resistance: not reported</td>
<td>Intervention&lt;br&gt;Mecillincam, 200 g, 1x per day for 25 days. <em>N</em>=38&lt;br&gt;Control group&lt;br&gt;Placebo. <em>N</em>=36</td>
<td>Length of follow-up: 28 days&lt;br&gt;Antibiotic resistance&lt;br&gt;Only 8% of <em>E. coli</em> strains were resistant to three or more antibiotics in the pre-travel samples. Post-travel, after participants had received either mecillinam or placebo, approximately 50% or more of the <em>E. coli</em> was resistant to more than three antibiotics</td>
<td>RCT Low methodological quality (0)</td>
</tr>
<tr>
<td><strong>Tannock 2011</strong>&lt;br&gt;RCT&lt;br&gt;Setting: Primary (14 long-term care facilities)&lt;br&gt;New Zealand&lt;br&gt;Dates not reported</td>
<td>To test the efficacy of probiotic strain <em>E. coli</em> Nissle 1917 in reducing the carriage of MDR <em>E. coli</em>&lt;br&gt;Participants&lt;br&gt;<em>N</em>=70&lt;br&gt;Age: not reported&lt;br&gt;Male: not reported, female: not reported&lt;br&gt;Inclusion criteria: not reported&lt;br&gt;Exclusion criteria: not reported</td>
<td>Bacteria: <em>E. coli</em>&lt;br&gt;Resistant to: fluoroquinolones (norfloxacin)&lt;br&gt;Mechanism of resistance: ESBL</td>
<td>Intervention&lt;br&gt;Probiotic: strain <em>E. coli</em> Nissle 1917, 5x10⁹-5x10¹⁰ CFU one capsule twice daily for five weeks. <em>N</em>=36&lt;br&gt;Control group&lt;br&gt;Placebo starch powder capsule. <em>N</em>=33</td>
<td>Length of follow-up: five weeks&lt;br&gt;Clinical success/improvement&lt;br&gt;There was no significant difference between the probiotic and placebo groups in the number of people with faecal and urine samples becoming negative or remaining positive.&lt;br&gt;Antibiotic resistance&lt;br&gt;103 norfloxacin-resistant <em>E. coli</em> isolates from 20 probiotic patients were tested for susceptibility. All isolates were resistant to norfloxacin (MIC &gt;256 µg/mL) and ciprofloxacin. The majority of norfloxacin-resistant <em>E. coli</em> isolates were MDR. The combination of MDRs differed</td>
<td>RCT Acceptable methodological quality (+)</td>
</tr>
<tr>
<td>Study details</td>
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<tr>
<td><strong>Wang 2009</strong></td>
<td>To report the effectiveness of extended-infusion meropenem compared with conventional bolus dosing in the management of HAP due to MDR <em>A. baumannii</em></td>
<td><strong>Bacteria</strong>: <em>A. baumannii</em></td>
<td><strong>Intervention</strong>&lt;br&gt;Extended intravenous meropenem infusion: 500 mg every 6 h over a 3-h infusion. <em>N</em>=15</td>
<td><strong>Clinical success/improvement</strong>&lt;br&gt;No significant differences were found between extended-infusion meropenem and conventional bolus dosing in the number of patients with treatment success at days 3, 5 and 7. The rates of relapse also did not significantly differ between the treatment groups.</td>
<td>RCT&lt;br&gt;Astonishing methodological quality (+)</td>
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<tr>
<td><strong>Setting</strong>&lt;br&gt;Tertiary (one ICU)&lt;br&gt;China&lt;br&gt;March 2006–July 2006</td>
<td><strong>Participants</strong>&lt;br&gt;<em>N</em>=30&lt;br&gt;Adults 19–45 years, middle aged 46–64 years, aged 65–79 years&lt;br&gt;Male: 19, female: 11&lt;br&gt;Inclusion criteria: HAP due to MDR <em>A. baumannii</em>&lt;br&gt;Exclusion criteria: not reported</td>
<td><strong>Resistance to</strong>: carbapenems (meropenem)</td>
<td><strong>Control group</strong>&lt;br&gt;Conventional treatment: intravenous meropenem 1 g. every 8 h over a 1-h infusion. <em>N</em>=15</td>
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<td><strong>Mechanism of resistance</strong>: not reported</td>
<td><strong>Length of follow-up</strong>: duration of treatment</td>
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<td><strong>Bacteria</strong>&lt;br&gt;<em>A. baumannii</em>&lt;br&gt;Resistant to: carbapenems (meropenem)</td>
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<td><strong>Intervention</strong>&lt;br&gt;Carbapenem restriction policy limiting the use of third-generation carbapenems. Only used when severe sepsis and after consultation with a physician from the Department of Infectious Diseases. <em>N</em>=12</td>
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<td><strong>Control group</strong>&lt;br&gt;Conventional treatment: no restrictions of carbapenem (doctors were able to prescribe if necessary). <em>N</em>=15</td>
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<td><strong>Xue 2009</strong></td>
<td>To determine the relation of carbapenem restriction with the incidence of MDR <em>A. baumannii</em> in VAP</td>
<td><strong>Bacteria</strong>: <em>A. baumannii</em>&lt;br&gt;Resistant to: carbapenems</td>
<td><strong>Intervention</strong>&lt;br&gt;Carbapenem restriction policy limiting the use of third-generation carbapenems. Only used when severe sepsis and after consultation with a physician from the Department of Infectious Diseases. <em>N</em>=12</td>
<td><strong>Mortality</strong>&lt;br&gt;The rates of mortality did not differ significantly between the treatment groups (RR 0.78; 95% CI 0.29–2.12).</td>
<td>RCT&lt;br&gt;Low methodological quality (0)</td>
</tr>
<tr>
<td><strong>Setting</strong>&lt;br&gt;Tertiary (one ICU)&lt;br&gt;China&lt;br&gt;June 2007–December 2007</td>
<td><strong>Participants</strong>&lt;br&gt;<em>N</em>=26&lt;br&gt;Adults 19–45 years, middle aged 46–64 years, aged 65–79 years&lt;br&gt;Male: 15, female: 11&lt;br&gt;Inclusion criteria: patients receiving mechanical ventilation for more than five days and diagnosed with VAP</td>
<td><strong>Resistance to</strong>: carbapenems</td>
<td><strong>Control group</strong>&lt;br&gt;Conventional treatment: no restrictions of carbapenem (doctors were able to prescribe if necessary). <em>N</em>=15</td>
<td><strong>Antibiotic resistance</strong>&lt;br&gt;More patients in the conventional group developed a carbapenem-resistant strain of <em>A. baumannii</em>, although the difference was not statistically significant (RR 0.63; 95% CI 0.38–1.04)</td>
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<td><strong>Mechanism of resistance</strong>: ESBL</td>
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<td>Exclusion criteria: not reported</td>
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<td>Length of follow-up: duration of treatment</td>
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*P. aeruginosa, Pseudomonas aeruginosa; E. coli, Escherichia coli; C. freundii, Citrobacter freundii; M. morgagnii, Morganella morgagnii; A. baumannii, Acinetobacter baumannii; A. anitratus, Acinetobacter anitratus; P. mira, Proteus mira; S.marcescens, Serratia marcescens; B. cepacia, Burkholderia cepacia; MDR, multi-drug resistant; VAP, ventilator-associated pneumonia; ESBL, extended-spectrum beta-lactamase; CMS, colistimethate sodium; RCT, randomized controlled trial; ICU, intensive care unit; UTI, urinary tract infection; HAP, hospital-acquired pneumonia; NSS, nebulized sterile normal saline; CFU, colony-forming unit; SD, standard deviation; RR, risk ratio; CI, confidence interval.*
4.4. Systematic Review References

4.4.1. Antimicrobial Stewardship


Lewis GJ, Fang X, Gooch M, Cook PP. Decreased resistance of *Pseudomonas aeruginosa* with restriction of ciprofloxacin in a large teaching hospital’s intensive care and intermediate care units. *Infect Control Hosp Epidemiol* 2012;33:368-373.


4.4.2. Other infection control measures


4.4.3. Selective decontamination


4.4.4. Treatment


4.5. Excluded clinical studies

4.5.1. Case–control study


Fortaleza CMCB, Freire MP, Filho Dde C, de Carvalho Ramos M. Risk factors for recovery of imipenem- or ceftazidime-resistant *Pseudomonas aeruginosa* among patients admitted to a teaching hospital in Brazil. *Infect Control Hosp.


4.5.2. Case series/report


4.5.3. Cross-sectional


Iosifidis E, Antachopoulos C, Tsivitanidou M, et al. Differential correlation between rates of antimicrobial drug


4.5.4. *In-vitro* studies


### 4.5.5. Prospective cohort


### 4.5.6. Surveillance


Behera B, Mathur P. High levels of antimicrobial resistance at a tertiary trauma care centre of India. *Ind J Med Res* 2011;133:343–345.


4.5.7. Narrative reviews, commentaries or editorials


Curcio D. Tigecycline for treating ventilator-associated pneumonia: a practical perspective. *Diagn Microbiol Infect Dis*
2011;69:466–467.


Wagenlehner FME, Schmiemann G, Hoyme U, et al. National S3 guideline on uncomplicated urinary tract infection:


### 4.5.8. Retrospective cohort


4.5.9. Study design not relevant


4.5.10. Controlled before–after studies without a minimum of two intervention and control sites


4.5.11. Interrupted time series studies without at least three data points before and after the intervention


4.5.12. Participants not relevant


Karageorgopoulos DE, Kelesidis T, Kelesidis I, Falagas ME. Tigecycline for the treatment of multidrug-resistant (including


### 4.5.13. Antibiotics used not relevant for the review


### 4.5.14. Not multi-drug-resistant infections


Appendix 5: CPD material

1. Which of the following are appropriate monotherapy meropenem-sparing agents:
   a) Temocillin
   b) Cefixime
   c) Ceftolozane/tazobactam
   d) Fosfomycin
   e) Ceftazidime/avibactam
   Answer a, c, d, e

2. Which of the following are true:
   a) Polymyxins do not require monitoring renal function in the elderly.
   b) Fluoroquinolones can be used to treat urinary infection due to multidrug resistant Gram-negative bacteria
   c) Oral pivmecillinam should be used alone in the treatment of upper urinary infection
   d) Polymyxins should be given in combination with other agents if they are used in treating carbapenem-resistant Enterobacteriaceae.
   e) Co-trimoxazole should be used in treatment of infections due to *Stenotrophomonas maltophilia*
   Answer b, d, e

3. Which of the following are true:
   a) In uncomplicated urinary infection due to a proven ESBL-producing organism, treatment is recommended for 3 days
   b) If infection with MDR GNB is suspected, treat asymptomatic bacteriuria
   c) Give antibiotic prophylaxis for urinary catheter insertion if previous history of symptomatic urinary infections associated with a catheter change or there is trauma during the catheter insertion
   d) Daily antibiotic prophylaxis is preferable to standby antibiotics in recurrent urinary infection
   e) Always send a urine specimen for culture if an antibiotic-resistant organism is suspected AND the patient is asymptomatic
Answer c, 

4. Which of the following are true;

   a) Ceftolozane-tazobactam is active against AmpC producing Enterobacteriaceae

   b) Ceftazidime-avibactam is active against AmpC producing# Enterobacteriaceae

   c) KPC-producing *Klebsiella sp.* often produce aminoglycoside methyltransferases conferring pan-aminoglycoside resistance

   d) NDM-producing *E. coli* are usually mecillinam susceptible

   e) *Proteus sp.* are usually resistant to fosfomycin

Answer b
Appendix 6: Consultation stakeholders

Antimicrobial Resistance and Hospital Acquired Infection

Advisory Committee (APRHAI)

British Medical Association

British Society of Antimicrobial Chemotherapy

British Infection Association

C. Diff Support

European Society of Clinical Microbiology and Infectious Diseases

Faculty of Intensive Care Medicine

Foundation Trust Network

Hand Hygiene Alliance

Healthcare Infection Society

Infection Prevention Society

Lee Spark Foundation

MRSA Action UK

NHS Confederation

NHS England

NHS Trust Development Authority

Patient’s Association

Public Health England/ Wales/ Scotland/ Northern Ireland

Royal College of Pathologists
Royal College of General Practitioners

Royal College of Nursing

Royal College of Physicians

Royal College of Surgeons

Service User Research Forum Healthcare acquired Infections

UK Clinical Pharmacists Association

Unison
## Appendix 7  Response from Stakeholders in consultation

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<tr>
<th>Respondent</th>
<th>Address</th>
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<th>Date Rec/d</th>
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<tbody>
<tr>
<td>Conor Doherty</td>
<td>NHS GGC – paed infectious diseases</td>
<td><a href="mailto:Conor.Doherty@ggc.scot.nhs.uk">Conor.Doherty@ggc.scot.nhs.uk</a></td>
<td>23 May 2016</td>
</tr>
<tr>
<td>Ibai Los-Arcos</td>
<td>Infectious Diseases Division, Hospital Universitari Vall d'Hebron Avda. Vall d'Hebron, 119-129 08035 Barcelona. Spain</td>
<td><a href="mailto:bai.losarcos@gmail.com">bai.losarcos@gmail.com</a></td>
<td>01 June 2016</td>
</tr>
<tr>
<td>Prof. Céline PULCINI</td>
<td>Nancy University Hospital, Nancy, France</td>
<td><a href="mailto:celine.pulcini@univ-lorraine.fr">celine.pulcini@univ-lorraine.fr</a></td>
<td>01 June 2016</td>
</tr>
<tr>
<td>Aaron Nagar</td>
<td>Microbiology Department, Antrim Area Hospital, 45 Bush Rd, Antrim, Northern Ireland, BT41 2RL</td>
<td><a href="mailto:Aaron.Nagar@northerntrust.hscni.net">Aaron.Nagar@northerntrust.hscni.net</a></td>
<td>01 June 2016</td>
</tr>
<tr>
<td>Dr Paul Chadwick &amp; Dr Alex Peel</td>
<td>Microbiology Department Salford Royal NHS Foundation Trust Stott Lane, Salford. M6 8HD</td>
<td><a href="mailto:paul.chadwick@srft.nhs.uk">paul.chadwick@srft.nhs.uk</a>; <a href="mailto:alex.peel@srft.nhs.uk">alex.peel@srft.nhs.uk</a></td>
<td>15 June 2016</td>
</tr>
<tr>
<td>Rebecca Tilley</td>
<td>West Suffolk NHS Foundation Trust, Hardwick Lane, Bury St Edmunds, Suffolk, IP33 2QZ.</td>
<td><a href="mailto:rebecca.tilley@wsh.nhs.uk">rebecca.tilley@wsh.nhs.uk</a></td>
<td>17 June 2016</td>
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<tr>
<td>Name</td>
<td>Organisation &amp; Address</td>
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<tr>
<td>Egidia Miftode</td>
<td>Hospital of Infectious Diseases Iasi Str O Botez no 2, code 700274, Iasi Romania</td>
<td><a href="mailto:emiftode@yahoo.co.uk">emiftode@yahoo.co.uk</a></td>
<td>27 June 2016</td>
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**British Society for Antimicrobial Chemotherapy**  
**Joint Working Party Paper on Multi resistant Gram-negative Infection: Treatment**

**Consultation deadline: Friday 17 June 2016**

- Please use this form for submitting your comments to BSAC. **COMMENTS WILL ONLY BE ACCEPTED ON THIS FORM**
- Please put each comment in a separate row
- Type directly onto the form. Do not paste other tables or figures as they may get lost
- Only comments received on the attached form will be considered.

**How to respond:** Please complete this BSAC response form and submit by email to fdrummond@bsac.org.uk no later than **Friday 17 June 2016**. Comments received after the deadline will not be accepted.

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Generally a very useful document. My one concern is that there is no mention of children, infants, neonates. Paeds are increasingly faced particularly with multiresistant G-ve UTI's and the data here is all from all adult studies/perspectives. Unfortunately experience with quite a few of the alternative drugs discussed here is very scant and often appropriate doses/formulations are unknown/unavailable.

1) As a result carabpenem sparing strategies are particularly problematic due to lack of alternatives. I would suggest that the doc either declares itself as ‘adult’ guidance or discusses this

2) Appropriate empirical treatment and prophylaxis strategies in the face of increasing trimethoprim resistance

Specific mention made that does not cover neonates and mostly does not deal with paediatric dosage or paediatric-specific issues such prophylaxis of UTIs.
for paed UTI's is a major issue and not discussed
British Society for Antimicrobial Chemotherapy
Joint Working Party Paper on Multi resistant Gram-negative Infection: Treatment

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References:

### British Society for Antimicrobial Chemotherapy

**Joint Working Party Paper on Multi resistant Gram-negative Infection: Treatment**

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<td>Nancy University Hospital, Nancy, France</td>
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<td>Phone number</td>
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Congratulations on your hard work!
I miss a summary of the recommended dosing and durations of treatment for each antibiotic and I feel that a section on optimised PK/PD (prolonged infusions...) would be a plus.

Dosing recommendations unless specifically otherwise referenced are as per product medicines license and outside scope of WP Report. Some information on prolonged infusion of meropenem now included but full section rather than illustration of benefit outside scope of WP.
<table>
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<tr>
<th>Name</th>
<th>Aaron Nagar</th>
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<tr>
<td>Organisation Address &amp; Postcode</td>
<td>Microbiology Department, Antrim Area Hospital, 45 Bush Rd, Antrim, Northern Ireland, BT41 2RL</td>
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<tr>
<td>Email</td>
<td><a href="mailto:Aaron.Nagar@northerntrust.hscni.net">Aaron.Nagar@northerntrust.hscni.net</a></td>
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Review is required to be evidence-based by NICE.
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<th>that it indicates preference. Feel that fosfomycin should be last as we may have to use the IV form more when CPE becomes more prevalent. It will not be useful if we drive resistance by PO fosfomycin overuse.</th>
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<td>Feel that we should remove 7 days treatment for uncomplicated UTI due to an ESBL producer. Exclude: Feel that clinical staff over treat older patients with asymptomatic bacteriuria and are always looking for excuses to extend duration. I feel we should stick with shorter durations for symptomatic cure. Comment is not evidence-based. WP specifically considered that bacteriologically optimum treatment required when MDR GNB being treated but not generally.</td>
</tr>
<tr>
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<td>81</td>
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<td>Feel that we should discourage dipstick use in patients over 65 years of age as per SIGN guidance. Exclude: Find it very difficult to convince clinicians not to use urine dipstick to diagnose and treat asymptomatic bacteriuria as UTI. Agree with specific point about asymptomatic bacteriuria and this has been added. Detailed technology review consideration of dipsticks in paper extended and changed.</td>
</tr>
</tbody>
</table>
| Name                           | Dr Paul Chadwick, Clinical lead/consultant microbiologist  
|                               | Dr Alex Peel, Antimicrobial stewardship lead/consultant microbiologist |
| Organisation Address & Postcode | Microbiology Department  
|                               | Salford Royal NHS Foundation Trust  
|                               | Stott Lane, Salford. M6 8HD |
| Email                         | paul.chadwick@srft.nhs.uk;  
<p>|                               | <a href="mailto:alex.peel@srft.nhs.uk">alex.peel@srft.nhs.uk</a> |
| Phone number                  | 01612065030 |
| Conflict(s) of Interest       |</p>
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<th>Changes:</th>
<th>WP Response</th>
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| Full     | general     |             | This guideline is welcomed as a resource to support treatment of MDR Gram negative infections and is supported by an extensive literature review. However, the recommendations in their current form appear as a fairly disjointed and inconsistent collection of statements. For example, the first recommendation starts with the role of temocillin vs Enterobacteria and Burkholderia and the second recommendation is for ampicillin-sulbactam vs Acinetobacter. This is not a logical or helpful sequence for presentation. Some of the recommendations appear as a surprise as they do not relate back to the preceding evidence or discussion. Care should be taken to ensure that this link is made and a justification provided for all recommendations.

Perhaps the functionality of the guideline could be improved with a more structured approach to the management of MDR Gram negatives? For example the role of each of the different classes of agents (recommended Y/N + comments) could be systematically presented as a table for each of the common resistance mechanisms, if necessary separated into different tables for the | Mark as “Exclude” OR “Include” (and reason for change or no change) | Very useful set of comments.

1. Antibiotics considered have been re-ordered to reflect important issues.
2. All recommendations checked for relationship to text and evidence.
3. Too many mechanisms to consider all but additional table on mechanisms and activity added. |
| Full | 28 | 783 | The conclusion that temocillin may be used as a carbapenem-sparing agent against Enterobacteria is (a reasonable) opinion of the authors but does not follow from the evidence presented. (The same opinion might also have be given for other classes of agent such as polymixins). Consideration should be given to simplifying and rephrasing the recommendation to ‘temocillin can be used to treat infections due to Enterobacteria, including ESBL and AmpC producers’ | Considered on a case by case basis |
| Full | 30 | 830 | The recommendation that ‘Amoxicillin-clavulanate should not be used to treat infection with known ESBL-producing organism unless sensitivity known ’ is generally not very helpful for a typical diagnostic laboratory where apparent co-amoxiclav susceptibility will be known either before or at the same time as ESBL production is confirmed. Alternatively, if the authors are suggesting that a patient with a history of ESBL positive UTI/infection should not be given co-amoxiclav until sensitivity for the current episode is confirmed, the recommendation should be clearly reworded | Detailed consideration given of this recommendation but given 6+% recurrence rate with ESBL infection previous susceptibility is an important factor in making this choice. Substantial caveats against use of coamoxiclav and piperacillin/tazobactam use in UK added both because of in vitro resistance and prevalence of OXA-1 in UK isolates |
| Full | 32 | 883 | The following recommendation is not supported by any evidence linking clinical outcomes to sepsis severity criteria: ‘Piperacillin-tazobactam can be considered for use in mild-moderate infections (i.e. not severe sepsis) due to ESBL-producing Enterobacteriaceae if supported by susceptibility results.’ The evidence should be provided, the opinion justified, or the recommendation removed. | Recommendation changed to omit reference to severity of infection |
| Full | 32 | 888 | The following recommendation is not supported by any evidence. ‘However combination with an aminoglycoside is advisable for severe infections.’ The evidence | Agree. Removed |
should be provided, the opinion justified, or the recommendation removed.

Full 36 986 It is unclear why there needs to be a separate recommendation for ertapenem: ‘Ertapenem is effective in treatment of infections with multi-resistant Enterobacteriaceae apart from carbapenemase producers’ when this has already been covered by the previous recommendation: ‘Carbapenems should be used to treat serious ESBL-producing Gram-negative infections subject to antibiotic stewardship to minimize the risk of developing resistance’.

Is there a reason why the general carbapenem recommendation is not extended to include AmpC resistance? For internal consistency within the document, we suggest merging these two recommendations as follow: ‘carbapenems can be used to treat infections due to ESBL or AmpC producing Enterobacteria’.

Full 37 1010 The format of the following recommendation is internally inconsistent within the document: ‘Although it retains good efficacy against infections with Pseudomonas aeruginosa, ceftazidime is not recommended for the treatment of other serious infections due to ESBL / AmpC producing Enterobacteriaceae, even if in vitro tests suggest the isolate is susceptible.’

We suggest 1) separating the recommendations for treating Pseudomonas and Enterobacterial infections, 2) rephrasing the recommendation for Enterobacteria as follows: ‘ceftazidime should NOT be used to treat infections due to ESBL or AmpC producing Enterobacteria’

Full 39 1074 Information relating to aztreonam-avibactam, while interesting, does not belong under a heading of ceftazidime-avibactam and is not

Ertapenem has different properties and is now recommended for OPAT. AmpC issue now considered

rephrased

Separate aztreonam section added whoich houses the experimental
<p>| Full | 40 | 1086 | The format of the following recommendation is internally inconsistent within the document: ‘With the exception of infections with metallo-β-lactamase strains, ceftazidime-avibactam, when available, should be used as alternative treatment to carbapenems’. We suggest rephrase this recommendation as follows: ‘ceftazidime-avibactam can be used to treat infections due to Enterobacteria, including ESBL and AmpC producers’ | Rewritten |
| Full | 42 | 1140 | The format of the following recommendation is internally inconsistent within the document (and implies that it should be used in preference to carbapenems): ‘Ceftolozane-tazobactam should be used as alternative treatment to carbapenems in treating ESBL-producing Gram negative pathogens (but not carbapenemase producers). We suggest rephrase this recommendation as follows: ‘ceftolozane-tazobactam can be used to treat infections due to Enterobacteria, including ESBL and AmpC producers’ | Rewritten |
| Full | 45 | 1231 | There is potential overlap/duplication regarding combination therapy with this recommendation and the recommendation on page 56, line1518. Consider either removing ‘and preferably used in combination with other agents’ and adding a cross reference to the later section | Cross-references inserted where useful |
| Full | 45 | 1234 | The recommendation with regard to renal function is internally inconsistent within the document as side effects are not systematically considered for other agents. Many important unwanted effects occur for many different antimicrobials and relevant monitoring should be considered as a matter of course by the prescribing clinician (and this might include monitoring colistin levels also, | To contain a;ready voluminous length Unwanted effects are highlighted where may be specifically over-looked. |</p>
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| Full | 46  | 1266   | The format of the following recommendation is internally inconsistent within the document: ‘Fluoroquinolones can be used to treat urinary infection due to multidrug resistant Gram-negative bacteria based on susceptibility results.’

We suggest rephrase this recommendation as follows: ‘quinolones can be used to treat complicated urinary tract infections due to Gram negative bacteria’                                                                                                                                                                                                                      | Standardised |
| Full | 51  | 1390   | The format of the following recommendation is internally inconsistent within the document: ‘Fosfomycin should be used in treatment of urinary infection due to multiresistant Gram-negative bacteria (oral administration only suitable for lower urinary infection)’

We suggest rephrase as follows: ‘Fosfomycin can be used to treat urinary tract infections due to Gram-negative bacteria (oral administration only suitable for lower urinary infection)’                                                                                                                                                                                                 | Standardised |
| Full | 52  | 1410   | To improve internal consistency within the document, we suggest adding the following additional recommendation (which follows from the preceding evidence): ‘aztreonam should NOT be used to treat infections due to ESBL or AmpC producing Enterobacteria’                                                                                                                                                                                                 | Agreed     |
| Full | 65  | 1758   | There is a recommendation to use 7 days therapy for ESBL simple UTIs to improve bacteriological clearance. There is no mention of clinical outcomes evidence. Bacteriological clearance does not necessarily correlate well with clinical outcomes (e.g. high prevalence of asymptomatic bacteriuria in certain patient populations). This recommendation could lead to a large increase in ab use if implemented widely and                                                                                                                                                                                                 | Debated at length within WP. Considered that best possible bacteriological clearance should be obtained with proven MDR GNB infection but caveat inserted about clinical relevance of bacteriological cure. |
it would need strong clinical evidence before doing so.

| Full | 66 | 1795 | This recommendation: ‘admission for intravenous aminoglycoside therapy’ is potentially confusing as it appears to exclude an inpatient carbapenem option (presumably temocillin or other agents recommended above for Enterobacteria could also be considered).

We suggest rephrase as ‘admission for intravenous therapy with an aminoglycoside or carbapenem (or temocillin etc)’ | Whole section for recommendations recast. Point accepted.

| Full | General | General | Although the evidence base is weak in many areas, and the authors are to be commended for covering many topic areas, we feel the document does not read like it is focused on an infection specialist dealing with ‘real world’ problems e.g. a patient with KPC bacteraemia with MICs of x,y,z and renal failure and obesity etc – we note that the US has produced flowcharts previously (e.g. Medscape http://www.medscape.com/viewarticle/780065_9) see screenshot on following page, and more recent publications - clearly these may be based on minimal evidence but they do provide a start. We wonder whether consideration could be given by the WP to producing similar tools. | “simple flow-charts inserted but subject is too diverse to deal with all possible clinical situations
Potential antibiotic combination therapy algorithm for the treatment of carbapenem-resistant Klebsiella pneumoniae infections stratified to site of infection and antibiotic results. *Algorithm would be appropriate for institution where >50% of isolates exhibit carbapenem MICs in the treatable range with HD therapy (MIC <32 mg/ml). Specific drugs used for empirical therapy should be tailored to the epidemiology of endemic carbapenem-resistant Klebsiella pneumoniae strains. **HD meropenem (5 g daily, administered as prolonged infusion). ***HD ticarcillin (200 mg loading dose, 100 mg once a day), see text regarding the limitations and evidence supporting the use of HD regimens. HD: High-dose.
British Society for Antimicrobial Chemotherapy  
Joint Working Party Paper on Multi resistant Gram-negative Infection: Treatment  

Consultation deadline: Friday 17 June 2016

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<table>
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<tr>
<th>Name</th>
<th>Rebecca Tilley</th>
</tr>
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<td>Organisation Address &amp; Postcode</td>
<td>West Suffolk NHS Foundation Trust, Hardwick Lane, Bury St Edmunds, Suffolk, IP33 2QZ.</td>
</tr>
<tr>
<td>Email</td>
<td><a href="mailto:rebecca.tilley@wsh.nhs.uk">rebecca.tilley@wsh.nhs.uk</a></td>
</tr>
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that is exasperated by the specifics within this DH requirement which seems to totally disregard all the improvements made in recent years with regard to C. difficile and antibiotic stewardship.

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<td>The document discusses using antibiotics such as temocillin, tigecycline, colistin and fosfomycin. EUCAST does not provide guidance on interpretation of temocillin susceptibility either by disk or MIC. Tigecycline needs to be tested via MIC for anything other than E coli. Fosfomycin &amp; colistin need to be tested by MIC. These requirements reduce the turnaround times for results. In addition, the turnaround times for CPE resistance mechanisms/additional sensitivities do not help support optimum patient management. Could PHE Colindale publish its testing methods/MIC interpretations to enable local testing rather than sending isolates to them? Is there a way to expedite EUCAST guidance on temocillin interpretations? Can BSAC offer recommendations to support local business cases for introducing technology that enables faster identification of e.g. CPEs in house as opposed to relying on reference laboratories?</td>
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In practice we now consider that molecular methodology is needed for colistin susceptibility testing and MICs for meropenem with MDR GNB and this has been added. To track the fast changing situation we have now recommended that i) mandatory reporting of carbapenem resistant isolates is introduced ii) isolates are dealt with expeditiously for patient benefit and iii) isolates referred where testing is beyond the scope of local laboratories.
British Society for Antimicrobial Chemotherapy
Joint Working Party Paper on Multi resistant Gram-negative Infection: Treatment

Consultation deadline: Friday 17 June 2016

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<td>Hospital of Infectious Diseases Iasi Str O Botez no 2, code 700274, Iasi Romania</td>
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<tr>
<td>Email</td>
<td><a href="mailto:emiftode@yahoo.co.uk">emiftode@yahoo.co.uk</a></td>
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**British Society for Antimicrobial Chemotherapy**  
**Joint Working Party Paper on Multi resistant Gram-negative Infection: Treatment**  

**Consultation deadline:** Friday 17 June 2016

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<td>Email</td>
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</tr>
<tr>
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<td>The referencing seems to be sporadic, with some areas very well referenced and others less so or not at all. A consistent approach throughout would be beneficial e.g. more references for UK statements in Pages 624-634</td>
<td>Include</td>
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<td>Evidence for translocation in absence of local infection is poor</td>
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<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>44</td>
<td>1211</td>
<td>Extra space required between 'toxicity' and ') (Huttner'</td>
<td>Include</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>46</td>
<td>1246</td>
<td>Extra space between 'quinolones' and ','</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>46</td>
<td>1255</td>
<td>Extra space between 'used' and 'to'</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>47</td>
<td>1276</td>
<td>Extra space between 'most' and 'Enterobacteriaceae'</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>48</td>
<td>1309</td>
<td>Extra space between ‘Tumbarello’ and ‘et al’</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>--------</td>
<td>-----</td>
<td>------</td>
<td>--------------------------------------------</td>
<td>---------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Full</td>
<td>49</td>
<td>1345</td>
<td>Extra space between ‘activity’ and ‘;’</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>50</td>
<td>1370</td>
<td>Extra space between ‘gentamicin’ and ‘(’</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>56</td>
<td>1518</td>
<td>Should ‘except rifampicin’ be included in the recommendation for combination therapy with colistin</td>
<td>Include</td>
<td>Considered but dealt with in text</td>
</tr>
<tr>
<td>Full</td>
<td>56-57</td>
<td>1539-1543</td>
<td>Is this truly accurate of UK practice. Internal work at St Thomas’ Hospital several years ago highlighted much higher resistance rates than this.</td>
<td>Include</td>
<td>Agree. Modified with additional references</td>
</tr>
<tr>
<td>Full</td>
<td>60</td>
<td>1624</td>
<td>Extra space between ‘GI’ and ‘effects’</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>60</td>
<td>1630</td>
<td>Extra space between ‘factors’ and ‘that’</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>56-63</td>
<td>N/A</td>
<td>Should there be a section on the use of sterilising agents or the use of NSAIDs in uncomplicated UTIs</td>
<td>Include</td>
<td>Probably not as emphasis is primarily on serious infection</td>
</tr>
<tr>
<td>Full</td>
<td>64</td>
<td>1738</td>
<td>Extra space between ‘cure’ and ‘Brayfield’</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>67</td>
<td>1824</td>
<td>Extra space between ‘or’ and ‘carbapenem’</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>67</td>
<td>1826</td>
<td>Extra space between ‘situations’ and ‘;’</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>68</td>
<td>1852</td>
<td>Extra space between ‘appropriate’ and ‘;’</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>68</td>
<td>1857</td>
<td>Extra space between ‘institutions’ and ‘;’</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>69</td>
<td>1862</td>
<td>Extra space between ‘and’ and ‘accounts’</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>70</td>
<td>1890</td>
<td>Extra space between ‘One’ and ‘controlled’</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>70</td>
<td>1892</td>
<td>Extra space between ‘most’ and ‘studies’</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>70</td>
<td>1898</td>
<td>Extra space between ‘trials’ and ‘;’</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>71</td>
<td>1917</td>
<td>Extra space between ‘few’ and ‘studies’</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>75</td>
<td>2011</td>
<td>Extra space between ‘of’ and ‘new’</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>76</td>
<td>2053</td>
<td>Extra space between ‘%’ and ‘absolute’</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>78</td>
<td>2088</td>
<td>Extra space required between ‘)’ and ‘in’</td>
<td>Include</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>78</td>
<td>2107</td>
<td>Extra space required between ‘bacteriuria’, which also needs an I removed, and ‘in’</td>
<td>Include/Exclude/Respell</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>78</td>
<td>2110</td>
<td>Extra space between ‘of’ and ‘colonisation’</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>80</td>
<td>2135</td>
<td>Extra space between ‘resistance’ and ‘;’</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>80</td>
<td>2147</td>
<td>Extra space between ‘resistance’ and ‘;’</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>80</td>
<td>2148</td>
<td>Extra space between ‘on’ and ‘consensus’</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>80</td>
<td>2147</td>
<td>Full stop needed after ‘i’</td>
<td>Include</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>81</td>
<td>2167</td>
<td>Extra space between ‘infection’ and ‘but’</td>
<td>Exclude</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>81-83</td>
<td>N/A</td>
<td>Should there again be a section on the use of sterilising agents or the use of NSAIDs in uncomplicated UTIs</td>
<td>Include</td>
<td>See previous response</td>
</tr>
<tr>
<td>Full</td>
<td>84</td>
<td>2217</td>
<td>Extra space required between ‘studies’ and ‘(SIGN’</td>
<td>Include</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>Full</td>
<td>85</td>
<td>2224</td>
<td>Extra space required between ‘grading’ and ‘(SIGN’, which is also superscripted unnecessarily</td>
<td>Include</td>
<td>Typos dealt with</td>
</tr>
<tr>
<td>------</td>
<td>-----</td>
<td>------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>--------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Full</td>
<td>85</td>
<td>2225</td>
<td>Table sometimes has full stop and at other times does not</td>
<td>Include</td>
<td>Hopefully dealt with</td>
</tr>
</tbody>
</table>