Prevention and control of multi-drug-resistant Gram-negative bacteria: recommendations from a Joint Working Party

Appendices A–E

Contents

Appendix A. Scope

1 Guideline title

Prevention and control of multi-drug-resistant Gram-negative bacteria: recommendations from a Joint Working Party

1.1 Short title

Control of multi-drug-resistant Gram-negative bacteria

2 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 Group, 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. The remit does not include management of cystic fibrosis or community outbreaks. Multi-drug resistance among Gram-negative bacteria will be defined as resistance to three or more of the following antimicrobials: ceftazidime, ciprofloxacin, meropenem, gentamicin or piperacillin/tazobactam. Consideration will be given to laboratory testing and susceptibility testing, although only screening and confirmatory tests available in a general microbiology laboratory and not those limited to reference laboratories. The use of antibiotic combinations in the therapy of infections will be considered, particularly oral combinations that can be used in the outpatient setting.

2.1 Population

2.1.1 Groups that will be covered

a) Adults

b) Children

c) Infections with the following organisms to evaluate the efficacy of antibiotics to treat community-acquired infections, and infections acquired in secondary or tertiary care that are caused by MDR Gram-negative bacteria.

Specific antibiotics: Whenever possible, antibiotics were separated as follows:

'Standard' antibiotics currently in use for which there is not much question on efficacy used as comparator: most cephalosporins, coamoxiclav, piperacillin/tazobactam quinolones, temocillin (pivmecillinam is the oral formulation of mecillinam).

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

Recently developed antibiotics: tigecycline, cefepime, few very new cephalosporins (e.g. ceftobiprole), the newest carbapenems or those in testing (e.g. doripenem).

Specific pathogens: *Escherichia coli*, *Klebsiella* spp. including *Klebsiella pneumoniae*, *Enterobacter* spp., *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Proteus* spp., *Serratia* spp., *Citrobacter freundii*, *Morganella morgagnii.*

2.1.2 Groups that will not be covered

Gonococci are Gram-negative and are increasingly resistant, but were excluded because relevant public health control actions are substantially different.

2.2 Healthcare setting

All settings in which National Health Service care is received.

2.3 Clinical management

2.3.1 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

2.3.2 Clinical issues that will not be covered

a) Sexually transmitted diseases

b) Cystic fibrosis

2.4 Main outcomes

Recommendations for practice

a) Surveillance
b) Screening
c) Prevention of transmission
d) Cleaning and environment

2.5 Economic aspects

In most areas, there are no anticipated additional costs unless existing practice falls well below currently accepted best practice. Failure to implement the recommendations would result in greater costs in terms of both economics and quality of life. 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.

2.6 Status

2.6.1 Scope

This is the final scope.

2.6.2 Timing

The development of the guideline recommendation will begin in July 2011.

3. Related NICE guidance

National Institute for Health and Care Excellence. *Infection: prevention and control of healthcare-associated infections in primary and community care.* NICE Clinical Guideline 139. London: NICE; 2012. Available at: http://www.nice.org.uk/guidance/cg139 [last accessed August 2014].

4. Further information

Guideline development process

Scottish Intercollegiate Guidelines Network. *SIGN 50: a guideline developer's handbook.* Revised edition. Edinburgh: Healthcare Improvement Scotland; 2014. Available at: http://www.sign.ac.uk [last accessed December 2014].

Appendix B. Declarations of interest

B.1 Introduction

All members of the Guideline Development Team, expert co-optees and all members of the National Clinical Guidance Centre staff were required to make formal declarations of interest at the outset, and these were updated throughout the development process. With one exception, no interests were declared that required any actions.

B.2 Peter Wilson (Secretary)

First meeting 24/11/11

Consultant on Drug Safety Monitoring Boards for Roche and Genentech, Advisory Panel for 3M

Second meeting 22/10/13, third meeting 12/12/13: no change

No action required

B.3 David Livermore

First meeting 24/11/11

Advisory boards or consultancy: Achaogen, Adenium, Alere, Allecra, AstraZeneca, Basilea, Bayer, BioVersys, Cubist, Curetis, Cycle, Discuva, Forest, GSK, Longitude, Meiji, Pfizer, Roche, Shionogi, Tetraphase, VenatoRx, Wockhardt. Paid lectures: AOP Orphan, AstraZeneca, Bruker, Curetis, Merck, Pfizer, Leo. Relevant shareholdings in Dechra, GSK, Merck, Perkin Elmer, Pfizer, collectively amounting to <10% of portfolio value

Second meeting 22/10/13, third meeting 12/12/13: did not attend

No action required

B.4 Beryl Oppenheim

First meeting 24/11/11

Advisory board: Astellas, Forrest. Lecture: Alere

Second meeting 22/10/13 did not attend, third meeting 12/12/13: no change

No action required

B.5 David Enoch
First meeting 24/11/11

ECCMID conference attendance: funded by Astellas and Eumedica

Second meeting 22/10/13 did not attend, third meeting 12/12/13: no change

No action required

B.6 Cliodna McNulty
First meeting 24/11/11

Travel expenses: Merieux Diagnostics

Second meeting 22/10/13, third meeting 12/12/13: no change

No action required

B.7 Jon Otter
First meeting 24/11/11 did not attend

Second meeting 22/10/13

Part-time employment at Bioquell. Paid lectures: 3M. Research funding: Pfizer and the Guy's & St Thomas' Charity

Third meeting 12/12/13: no change

Dr Otter did not take part in the section related to the environment, and restricted his advice to that on behalf of the Infection Prevention Society

B.8 Maria Cann
First meeting 24/11/11 did not attend

IPS conference attendance: funded by corporate sponsorship from Mölnlycke Healthcare

Second meeting 22/10/13, third meeting 12/12/13: no change

No action required

B.9 Peter Jenks
First meeting 24/11/11

Advisory Board: Baxter

Second meeting 22/10/13, third meeting 12/12/13: did not attend

No action required

No declared conflict of interests for the other participants

Appendix C. Clinical evidence tables

Antibiotic stewardship

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Ben-David 2010 ITS **Setting** Tertiary (one hospital) Israel January 2006–December 2008	To assess the effect of an intensified intervention, that included active surveillance, on the incidence of infection with carbapenem-resistant *K. pneumoniae* **Participants** *N*=390 Age: not reported Male: not reported, female: not reported Inclusion criteria: data from medical records of all patients who acquired CRKP infection Exclusion criteria: not reported	**Bacteria**: *K. pneumoniae* **Resistant to**: carbapenems, cephalosporins, fluoroquinolones, trimethoprim-sulfamethoxazole **Mechanism of resistance**: not reported	**Intervention** 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 2. Active surveillence 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 **Length of pre-intervention**: 17 months prior **Length of post-intervention**: 19 months following	**Infection control** Before the intervention, the incidence of clinical infection with CRKP had increased 6.42-fold to 6.93 cases per 10,000 patient-days 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 (*P*<0.001). The slope significantly changed with the introduction of the intervention from 0.12 to -0.07 (*P*<0.001)	**ITS** **Protection against secular changes (high quality)** **Protection against detection bias (acceptable quality)**
Borer 2011 ITS **Setting**	To devise a local strategy for eradication of a hospital-wide outbreak caused by CRKP **Participants**	**Bacteria**: *K. pneumoniae* **Resistant to**: carbapenems	**Intervention** 1. Emergency department flagging system 2. Building of a cohort space or ward	**Bacterial colonization and infection** During the intervention, the CRKP undetected ratio showed a significant increase from 55.7% for June–	**ITS** **Protection against secular changes (high quality)**

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Tertiary (one hospital) Israel May 2006– May 2010	*N*=803 Adolescents 13–18 years, adults 19–45 years, middle aged 46–64 years, aged 65–79 years, elderly 80+years Male: 410, female: 393 Inclusion criteria: data from medical records of patients with CRKP infection Exclusion criteria: not reported	**Mechanism of resistance**: not reported	3. Intensive active surveillance in high-risk wards 4. Epidemiological investigations 5. Carbapenem-restriction policy **Length of pre-intervention**: 11 months prior **Length of post-intervention**: 36 months following	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*<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). **Antibiotic use** Meropenem use showed a statistically significant decrease from 2007 to 2010 (*P*≤0.001); colistin use increased significantly during the same period (*P*≤0.001)	**Protection against detection bias (acceptable to low quality)**
Church 2011 ITS **Setting** Secondary (one hospital) USA January	To assess the possible effects of varying usage of levofloxacin, gatifloxacin and moxifloxacin on *P. aeruginosa* susceptibility to piperacillin-tazobactam, cefepime and tobramycin **Participants** *N*: not reported Age: not reported Male: not reported, female: not reported	**Bacteria**: *P. aeruginosa* **Resistant to:** aminoglycosides (tobramycin), cephalosporins (cefepime), piperacillin/tazobactam **Mechanism of resistance**: not reported	**Intervention** 1. Levofloxacin replaced with gatifloxacin in 2001 2. Gatifloxacin replaced with moxifloxacin in 2006 Ciprofloxacin available throughout study period **Length of pre-intervention**: 15 months prior **Length of post-intervention 1**: 60 months	**Antibiotic resistance and susceptibility** No association between the susceptibility of *P. aeruginosa* 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 moxifloxacin (*P*=0.0571). In the case of piperacillin/tazobactam, a positive change in susceptibility over time	**ITS** Protection against secular changes (low quality) Protection against detection bias (low quality)

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
2000-December 2008	Inclusion criteria: data from clinical microbiology and pharmacy databases of the Medical University of South Carolina Medical Centre Exclusion criteria: not reported		**Length of post-intervention 2**: 30 months following	was detected after introduction of moxifloxacin (*P*=0.0589). In each analysis, the effect of total fluoroquinolone usage was not significant	
Cohen 2011 ITS **Setting** Tertiary (one hospital) Israel March 2006–August 2010	To describe the implementation of an institution-wide, multiple-step intervention to curtail the epidemic spread of CRKP **Participants** *N*=33,570 Age: not reported Male: not reported, female: not reported Inclusion criteria: all patients affected by CRKP Exclusion criteria: not reported	**Bacteria**: *K. pneumoniae* **Resistant to**: carbapenems **Mechanism of resistance**: not reported	**Intervention** 1. Single-room isolation and contact precautions 2. Cohorting 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 3. Weekly active surveillance in the ICU 4. Active surveillance of patients on admission to the emergency department **Length of pre-intervention:** not reported **Length of post-intervention 1**: 14 months **Length of post-intervention 2**: 39 months **Length of post-intervention 3**: 2 years **Length of post-intervention 4**: 15 months	**Bacterial colonization and infection** 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 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) In the emergency department, the mean rate of compliance with the active surveillance protocol (± SD) was 43% ± 10%	**ITS** **Protection against secular changes (high quality)** **Protection against detection bias (acceptable to low quality)**
Dortch 2011	To examine the effect of the	**Bacteria**: *P.*	**Intervention**	**Antibiotic use**	**ITS**

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
ITS **Setting** Tertiary (one TICU, one SICU) USA January 2001–December 2008	antibiotic stewardship programme on the incidence of resistant Gram-negative HAIs **Participants** SICU *N*=6044, TICU *N*=14,802 Adults 19–45 years, middle aged 46–64 years, aged 65–79 years Male: 14,277, female: 6569 Inclusion criteria: all patients admitted to the SICU or TICU during the study period who contracted an HAI with microbiological confirmation of at least one Gram-negative pathogen, at least 18 years of age Exclusion criteria: not reported	*aeruginosa, Acinetobacter* spp. **Resistant to**: aminoglycosides, carbapenems, cephalosporins (third- and fourth-generation), fluoroquinolones **Mechanism of resistance**: not reported	1. Antibiotic stewardship: April 2002, guidelines for prophylactic antibiotics were devised for select procedures 2. Antibiotic rotation: January 2005, institution-wide initiative for surgical prophylaxis based on the Surgical Care Improvement Project **Length of pre-intervention**: 15 months **Length of post-intervention 1**: 11 months **Length of post-intervention 2**: 16 months	Both in the SICU and TICU and there was a significant decrease in the utilization of total broad-spectrum antibiotics (BLIC, carbapenems, fluoroquinolones, third- and fourth-generation cephalosporins) targeting Gram-negative pathogens over the observation period (*P*<0.001) **Infection** During the 8-year observation period, the proportion of healthcare-associated infections caused by MDR Gram-negative pathogens decreased from 37.4% (2001) to 8.5% (2008), whereas the proportion of healthcare-associated infections caused by pan-sensitive pathogens increased from 34.1% to 53.2%	**Protection against secular changes (high quality)** **Protection against detection bias (acceptable to low quality)**
Lewis 2012 ITS **Setting** Tertiary (11 ICUs and immediate care units) USA January 2004–December 2010	To examine the effect of restricting ciprofloxacin use on the resistance of nosocomial Gram-negative bacilli, including *P. aeruginosa*, to group 2 carbapenems in a hospital's ICUs and intermediate care units **Participants** *N:* not reported Age: not reported Male: not reported, female: not reported Inclusion criteria: all clinical ICU and intermediate care unit specimens	**Bacteria**: *E. aerogenes, E. cloacae, P. aeruginosa, A. baumannii* **Resistant to**: carbapenems (imipenem, meropenem, doripenem), cephalosporins (cefepime), piperacillin/tazobactam, fluoroquinolones (ciprofloxacin)	**Intervention** Restriction of ciprofloxacin: ciprofloxacin use was restricted hospital wide in July 2007; after this restriction, pre-approval by the on-call infectious diseases fellow was required for its use **Length of pre-intervention**: 42 months **Length of post-intervention**: 42 months	**Antibiotic use** Following the restriction of ciprofloxacin, there was a significant decreasing trend (*P*=0.0027) in its use, from 87.09 DDD/1000 patient-days in 2004 to 8.04 DDD/1000 patient-days in 2010. Use of the group 2 carbapenems increased significantly (*P*=0.0134) from 11.96 DDD/1000 patient-days in 2004 to 28.19 DDD/1000 patient-days in 2010. Overall, there was a hospital-wide decrease of 18.4% (*P*<0.0001) in the use of antibacterials during the study time	**ITS** **Protection against secular changes (high quality)** **Protection against detection bias (acceptable quality)**

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	(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.	**Mechanism of resistance**: not reported		**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 January 2002–December 2006	To test whether reduction of third-generation cephalosporin use has a sustainable positive impact on the high endemic prevalence of third generation cephalosporin-resistant *K. pneumoniae* and *E. coli* in an ICU **Participants** *N*=3758 Age: not reported Male: not reported, female: not reported Inclusion criteria: 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/or 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-abominal infections was switched from third-generation cephalosporins to piperacillin in combination with a beta-lactamase	**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, R^2=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, R^2=0.378) and in the use of imidazoles (-94.5 DDD/1000, 95% CI -121.2 to -67.7, R^2=0.463)	**ITS** **Protection against secular changes (high quality)** **Protection against detection bias (high quality)**

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	Exclusion criteria: not reported		inhibitor. The duration of antibiotic therapy for open fractures was shortened to single-shot pre-operative prophylaxis **Length of pre-intervention**: 30 months **Length of post-intervention**: 30 months	The use of aminoglycosides decreased steadily before and after the intervention (slope -1.4 DDD/1000 patient-days per month, 95% CI -1.8 to -1.0, R^2=0.430); piperacillin and piperacillin/tazobactam showed a significant increase in level of 64.4 DDD/1000 patient-days (95% CI 38.5–90.3) and continued to increase by 2.3 DDD/1000 patient-days (95% CI 1.0–3.6) per month after the intervention (R^2=0.745)	
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** *N*=11,887 Age: not reported Male: not reported, female: not reported Inclusion criteria: monthly data on antimicrobial use obtained from the computerized pharmacy database. Monthly resistance data collected from the microbiology laboratory. Only samples taken in the ICU were considered Exclusion criteria: copy strains – defined as an isolate of the same	**Bacteria**: *E. coli, K. pneumoniae, P. aeruginosa* **Resistant to**: carbapenems (imipenem), cephalosporins (third-generation) **Mechanism of resistance**: not reported	**Intervention** Change in antibiotic prophylaxis: Revised recommendation of single-shot prophylaxis with cefuroxime for shunt catheters, beginning in January 2004 **Length of pre-intervention**: 24 months prior **Length of post-intervention**: 36 months following	**Antibiotic use** 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. The reduction in total antibiotic consumption was sustainable and did not increase over the next 36 months.	**ITS** **Protection against secular changes (high quality)** **Protection against detection bias (acceptable quality)**

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	species showing the same susceptibility pattern throughout a 1-month period in the same patient, no matter what the site of isolation				
Yong 2010 ITS **Setting** Tertiary (one ICU) Australia January 2000–December 2006	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 **Participants** *N*=13,295 Age: not reported Male: not reported, female: not reported Inclusion criteria: not reported Exclusion criteria: not reported	**Bacteria**: *E. coli, Klebsiella* spp., *Enterobacter* spp., *P. aeruginosa, Acinetobacter* spp. **Resistant to**: aminoglycosides, carbapenems (imipenem), cephalosporins (ceftazidime), fluoroquinolones (ciprofloxacin) **Mechanism of resistance**: not reported	**Intervention** 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 **Length of pre-intervention**: 30 months **Length of post-intervention**: 54 months	**Antibiotic use** 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. 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) **ICU antibiotic consumption** The use of antibiotics to cover Gram-negative bacteria in the ICU, including third- and fourth-generation cephalosporins, carbapenems, extended-spectrum penicillins,	**ITS** **Protection against secular changes (high quality)** **Protection against detection bias (acceptable to low quality)**

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
				aminoglycosides and fluoroquinolones remained stable during the study period	
Xue 2009 RCT **Setting** Tertiary (one ICU) China June 2007–December 2007	To determine the relation of carbapenem restriction with the incidence of MDR *A. baumannii* in VAP **Participants** *N*=26 Adults 19–45 years, middle aged 46–64 years, aged 65–79 years Male: 15, female: 11 Inclusion criteria: Patients receiving mechanical ventilation for more than five days and diagnosed with VAP Exclusion criteria: not reported	**Bacteria**: *A. baumanniii* **Resistant to**: carbapenems **Mechanism of resistance**: ESBL	**Intervention** 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. *N*=12 **Control group** Conventional treatment: no restrictions of carbapenem (doctors were able to prescribe if necessary). *N*=15 **Length of follow-up**: duration of treatment	**Mortality** Mortality rates did not differ significantly between the treatment groups (RR 0.78; 95% CI 0.29–2.12). **Antibiotic resistance** More patients in the conventional group developed a carbapenem-resistant strain of *A. baumannii*, although the difference was not statistically significant (RR 0.63; 95% CI 0.38–1.04)	**RCT** Low methodological quality (0) Small sample size

K. pneumoniae, Klebsiella pneumonia; P.aeruginosa, Pseudomonas aeruginosa; A. baumanniii, Acinetobacter baumanniii; 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.

Other infection control measures

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Levin 2010 CBA **Setting** Tertiary (two ICUs) Israel Dates not reported	To analyse whether single patient rooms in the ICU decreased bacterial transmission between ICU patients **Participants** *N*=207 Age: not reported Male: not reported, female: not reported Inclusion criteria: not reported Exclusion criteria: not reported	**Bacteria**: *Acinetobacter* spp., other Gram-negative bacteria **Resistant to**: carbapenems **Mechanism of resistance**: ESBL	**Intervention** ICU A converted to single patient rooms. Old ICU A *N*=64, new ICU A *N*=62 **Control group** ICU B remained open plan. Old ICU B *N*=44, new ICU B *N*=39 **Length of follow-up**: not reported	**Infection control** 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, *P*=0.043], which was confirmed using survival analysis (*P*=0.011). ICU B showed no changes over the study	**CBA** Low methodological quality (0)

ICU, intensive care unit; ESBL, extended-spectrum beta-lactamase; CBA, controlled before–after study.

Selective decontamination

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Agusti 2002 Quasi-randomized	To determine the efficacy of SDD in patients with multi-drug-resistant *A. baumannii* intestinal colonization **Participants**	**Bacteria**: *A. baumannii* **Resistant to**: aminoglycosides (tobramycine)	**Intervention** SDD: a combination of polymyxin E (colistin) (150 mg) and tobramycine (80 mg) administered in 20-mL liquid	**Bacterial colonization** Rates of faecal, pharyngeal and axillary colonization did not significantly reduce during ICU stay in the control group (*P* value not	**Quasi-randomized** Low methodological quality (0)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Setting Tertiary (one ICU) Spain October 1998–June 1999	*N*=54 Adults 19–45 years, middle aged 46–64 years, aged 65–79 years Male: 16, female: 5 Inclusion criteria: Intervention group 1. All patients with *A. baumannii* fecal colonization 2. An expected ICU stay exceeding five days Control group 1. All patients admitted 1 October–30 Novembe 1998 with *A. baumannii* faecal colonization 2. At least one series of axillary-pharyngeal-rectal swab performed Exclusion criteria: not reported	**Mechanism of resistance**: not reported	form x 4/day (orally or through nasogastric tube), and 0.5 g of gel containing 2% of colistin and tobramycine applied round the gum margins and oropharynx x 4/day. Duration of treatment from detection of *A. baumannii* to discharge from ICU. *N*=21 **Control group** No intervention. *N*=33 **Length of follow-up**: duration of treatment	reported). In the SDD group, the rate of faecal and pharyngeal carriage was reduced significantly (*P*<0.001 and *P*=0.003, respectively), but not the rate of cutaneous carriage **Antibiotic resistance** MDR *A. baumannii* had not been detected at the time of faecal carriage in 21 of 33 (63.6%) of the control group and 11 of 21 (52.3%) of the SDD group. In the SDD group, all *A. baumannii* strains were tobramycin resistant and susceptible to colistin at the beginning of the study. No resistance to colistin developed during the study	Small sample size
Brun-Buisson 1989 Quasi-randomized **Setting** Tertiary (one ICU) France January 1987-May 1987	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. **Participants** *N*=86 Adults 19–45 years, middle aged 46–64 years, aged 65–79 years Male: not reported, female: not reported	**Bacteria**: *Enterobacter* spp., *P. aeruginosa* **Resistant to**: aminoglycosides (amikacin), third-generation cephalosporins **Mechanism of resistance**: ESBL	**Intervention** 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 **Control group** No prophylaxis. *N*=50 **Length of follow-up**: not	**Mortality** All-cause mortality and mortality from nosocomial infections did not differ significantly between patients receiving SDD or no prophylaxis **Clinical success/improvement** There was no significant difference between patients receiving SDD or no prophylaxis in: – the incidence of any nosocomial infection – the infections caused by Gram-negative bacteria	**Quasi-randomized** Low methodological quality (0)

Study details	Objective and participants	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		reported	– 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	
Saidel-Odes 2012 RCT **Setting** Tertiary (one internal medicine ward) Israel November	To assess the effectiveness of SDD for eradicating CRKP oropharyngeal and gastrointestinal carriage **Participants** *N*=40 Middle aged 46–64 years, aged 65–79 years, elderly 80+ 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)	**RCT** High methodological quality (++) Small sample size

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
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 and/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 **Length of follow-up**: six weeks	**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.

Systematic reviews

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Falagas 2009[1] **Setting** International Search up to January 2009	To assess the clinical and microbiological effectiveness of fosfomycin in the treatment of MDR, XDR or PDR non-fermenting Gram-negative bacterial infections **Participants** *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 *Pseudomonas* spp., *Acinetobacter* spp., *Stenotrophomonas* spp. and *Burkholderia* 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.	**Bacteria**: *Pseudomonas* spp., *Acinetobacter* spp., *Stenotrophomonas* spp. and *Burkholderia* spp. See Table II in the paper for details of clinical studies	**Intervention** Fosfomycin **Control group** Combination of fosfomycin with other antimicrobial agents	**Microbiological**: a total of 1859 MDR non-fermenting Gram-negative isolates. Susceptibility rate to fosfomycin of MDR *P. aeruginosa* isolates was ≥90% and 50–90% in 7/19 and 4/19 relevant studies, respectively. 30.2% isolates of MDR *P. aeruginosa*, 3.5% MDR *A. baumannii* isolates were found to be susceptible to fosfomycin **Clinical**: 91% of the patients clinically improved (treatment of infections caused by MDR *P. aeruginosa*)	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

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	Studies representing abstracts in scientific conferences				
Falagas 2009[2] **Setting** Not reported Searches performed: 9 July 2008, 16 July 2008 and 11 September 2008	To evaluate the available clinical evidence regarding the effectiveness and safety of systemic colistin in children without cystic fibrosis **Participants** *N*=370 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. pyocyanin, 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 one week after withdrawal of	Acceptable methodological quality (+) This review was included because it is on the topic; however, the conclusions reached are not supported by the study design

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
				colistin: 16/44 2. Proteinuria, disappearing right after colistin withdrawal: 14/44 3. Oliguria during the initial stages of colistin treatment: 1/44 4. No adverse events: 13/44	
Falagas 2010[3] **Setting** International Searches up to January 2009	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 **Participants** *N*=119 Studies: 17 in-vitro microbiological studies, two prospective studies, one retrospective study and two case reports Inclusion criteria: studies on Enterobacteriaceae isolates with an advanced drug resistance (MDR, carbapenem resistance, or production of ESBLs, AmpC β-lactamases, serine carbapenemases or metallo-β-lactamases) profile and their susceptibility to fosfomycin, and the clinical effectiveness of treatment with fosfomycin for infections with these pathogens Exclusion criteria: abstracts in	**Bacteria***:* **Microbiological studies** *K. pneumoniae isolates, E. coli* **Clinical studies** *E. coli, S. typhimurium, S. typhi* See Table III in the paper for details of studies	**Intervention** Amoxicillin-clavulanate potassium **Control group** Fosfomycin–trometamol in two of the *E. coli* studies	**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 *E. coli* (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 *Salmonella* spp. Reported treatment was effective with fosfomycin	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

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	scientific conferences or studies published in languages other than English, Spanish, French, German, Italian or Greek				
Falagas 2012[4] **Setting** Not reported Searches from 2000 to 2010	To identify and evaluate the available data regarding the susceptibility of recent Gram-negative bacteria to isepamicin, including that of MDR strains of bacteria **Participants** *N*=512 Studies=11 microbiological, one RCT, one prospective study, one restrospective study Inclusion 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 Exclusion criteria: studies that examined a sample of fewer than 10 isolates or patients, studies referring	**Bacteria:** **Clinical studies** *S. epidermidis, E. coli, S. pneumoniae, P. aeruginosa* See Table II in the paper for details of studies	**Intervention** Isepamicin **Control group** Two clinical studies – amikacin one clinical study – isepamicin + levofloxacin for prophylaxis	**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 **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%	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

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	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				
Kaki 2011[5] **Setting** International Search January 1996 to December 2010	To evaluate the current state of evidence for antimicrobial stewardship interventions in the critical care unit **Participants** *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 patients. Additionally, antibiotic	**Bacteria:** *P. aeruginosa,* *A. baumannii,* *E. coli,* *Klebsiella* spp., ESBL See Table I in the paper for details of studies.	**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 **Control group** Not reported, presumably no stewardship	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 Antibiotic stewardship was not associated with increases in nosocomial infection rates, length of stay or mortality	High methodological quality (++)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	cycling. Conference abstracts				
Siempos 2007[6] **Setting** Not reported Search January 1950 to March 2006	To clarify whether carbapenems are more effective and/or safer than other broad-spectrum antibiotics for the empirical treatment of patients with HAP **Participants** *N*=2731 Studies: 12 RCTs Inclusion criteria: randomized controlled clinical trial; studied the role of carbapenems in comparison with other broad-spectrum antibiotics or a combination of antibiotics for the empirical treatment of patients with HAP; assessed the effectiveness, toxicity and/or mortality of both therapeutic regimens. Included both patients with HAP and patients with community-acquired pneumonia; however, only data regarding patients with HAP were extracted. Trials with both blind and unblind design were included, and only RCTs written in English, French and German Exclusion criteria: RCTs conducted primarily in neutropenic patients with solid organ tumours or	**Bacteria:** *P. aeruginosa* See Table I in the paper for details of studies	**Intervention** Carbapenems: 1. Imipenem/ cilastatin (eight studies) 2. Meropenem (four studies) **Control group** Imipenem/ cilastatin compared with: 1. Fluoroquinolones: levofloxacin, ciprofloxacin (three studies) 2. Other beta-lactams: piperacillin/tazobactam, aztreonam, cefepime, ceftazidime (five studies) Meropenem compared with: combination of a cephalosporin (ceftazidime, cefuroxime) with an aminoglycoside (amikacin, gentamicin, tobramycin)	1. All-cause mortality: lower mortality in the carbapenems group (OR 0.72, 95% CI 0.55–0.95) 2. Treatment success (clinical): no difference between groups (OR 1.08, 95% CI 0.91–1.29) 3. Treatment success (microbiological): no difference between groups (OR 1.04, 95% CI 0.72–1.50) 4. Adverse effects: no difference (0.81, 0.46–1.43) *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 carbamenems group. Late onset of HAP subgroup: no difference between groups (OR 1.34, 95% CI 0.91–1.97)	High methodological quality (++)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	haematological malignancies and trials that included fewer than 10 patients with pneumonia who received a carbapenem. Experimental trials and trials focusing on pharmacokinetic and/or pharmacodynamics parameters. Finally, RCTs comparing the effectiveness and safety of two different carbapenems				

P. aeruginosa, Pseudomonas aeruginosa; A. baumannii, Acinetobacter baumannii; K. aerogenes, Klebsiella aerogenes; H. influenza, Haemophilus influenza; P. pyocyanin, Pseudomonas pyocyanin; 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. epidermidis, 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.

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Treatment

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Betrosian 2007 RCT **Setting** Tertiary (1 ICU) Greece October 2004–February 2006	To evaluate the clinical efficacy and safety of high-dose regimen ampicillin sulbactam for the treatment of VAP from MDR *A. baumannii* **Participants** *N*=27 Age: not reported Male: 15, female: *N*=12 Inclusion criteria: all patients mechanically ventilated for more than 72 h with positive tracheal aspirates for *A. baumannii* Exclusion criteria: episodes of VAP in which *A. baumannii* was isolated in conjunction with another micro-organism	**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 **Length of follow-up**: one month	**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) Very small sample size
Betrosian 2008	To compare the clinical efficacy and safety of high-dose ampicillin/sulbactam vs colistin as	**Bacteria**: *A. baumannii* **Resistant to**:	**Intervention** Colistin, intravenous 3 MIU every 8 h for eight to 10 days.	**Mortality** 14-day VAP mortality and 28-day all-cause mortality were not significantly	**RCT** Low methodological

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
RCT **Setting** Tertiary (2 ICUs) Greece Dates not reported	monotherapy for the treatment of *Acinetobacter* spp. VAP **Participants** *N*=28 Middle aged 46–64 years, aged 65–79 years Male: 14, female: 14 Inclusion criteria: ventilated patients for >72 h who developed MDR *A. baumannii* VAP Exclusion criteria: cases of VAP with mixed isolated micro-organisms, combination antibiotic therapy, allergy to beta-lactamase or penicillin, or previous enrolment in similar studies	Aminoglycosides, carbapenems, cephalosporins, fluoroquinolones **Mechanism of resistance**: not reported	*N*=15 **Control group** Ampicillin/sulbactam, 9 g (at a rate 2:1) every 8 h for eight to 10 days, administered as follows: three vials (20 mL each) containing 3.0 g of ampicillin/sulbactam diluted in 200 mL of 5% dextrose provided within 1-h duration infusion. *N*=13 **Length of follow-up**: two-week- and one-month mortalities	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) or bacteriological failure (persistence of *A. baumannii* isolates (>104 CFU/mL) **Adverse events** There was no difference in the adverse effects experienced by participants	quality (0) Small sample size
Chastre 2003 RCT **Setting** Tertiary (51 ICUs) France May 1999-June 2002	To compare the efficacy of eight days vs 15 days of antibiotic treatment of patients with microbiologically proven VAP **Participants** *N*=401 Middle aged 46–64 years, aged 65–79 years Male: 141, female: 46 Inclusion criteria: 1. >18 years of age 2. Clinical suspicion of VAP 3. Positive quantitative cultures of	**Bacteria**: *E. coli, Klebsiella* spp., *Enterobacter* spp., *P. aeruginosa, Acinetobacter* spp., *Proteus spp., Serratia spp., C. freundii, M. morgagnii* **Resistant to**: ticarcillin, methicillin **Mechanism of resistance**: ESBL	**Intervention** Antibiotics for eight 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 antimicribial agent. *N*=197	**Mortality** 28-day and 60-day all-cause mortality and in-hospital mortality did not significantly differ between the eight- and 15-day regimes **Clinical success/improvement** Risk differences (90% CIs) to develop an unfavourable outcome (defined as death, pulmonary infection recurrence, or prescription of a new antibiotic for any reason provided for ≥48 h) were not significantly different between the eight- and 15-day regimes for all	**RCT** High methodological quality (++)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	distal pulmonary secretion samples 4. Instigation within the 24 h following of appropriate empirical antibiotic therapy directed against the micro-organism/s responsible for the infection Exclusion criteria: 1. Pregnant 2. Enrolled in another trial 3. Little chance of survival 4. Neutropenia 5. Concomitant acquired immunodiffeciency syndrome 6. Immunosuppressants or long-term corticosteroid therapy 7. Concomitant extrapulmonary infection that required prolonged antimicrobial treatment 8. Attending physical declined full-life support. 9. Early-onset pneumonia (within the first five days of mechanical ventilation) and no antimicrobial therapy during the 15 days preceding infection.		**Control group** 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 antimicribial agent. *N*=204 **Length of follow-up**: three months	patients (RR 2.6, 90% CI -5.6 to 10.7) and for those patients with non-fermenting Gram-negative bacteria (RR 8.6, 90% CI -5.9 to 23.1) 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. **Antibiotic use** 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. 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 **Antibiotic resistance** 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	

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
				infections, respectively; *P*=0.04)	
Cox 1987 RCT **Setting** Secondary (two hospitals) USA March 1985–December 1985	To compare the efficacy of norfloxacin vs standard parenteral treatment of non-bacteraemic, hospital-acquired UTI **Participants** *N*=104 Age: not reported Male: not reported, female: not reported Inclusion criteria: 1. Hospitalized patients 2. >18 years of age 3. Documented UTI caused by an organism known or presumed susceptible to norfloxacin Exclusion criteria: 1. <18 years of age 2. Pregnant or not practising an effective means of birth control 3. A history of allergic diathesis or an allergy to nalidixic acid, oxolinic acid or norfloxacin 4. Functional renal abnormalities or unstable deteriorating renal function 5. Comatose or high probability of imminent death 6. Serious concurrent infection 7. Treated or recently completed treatment with antibiotics 8. History or visual disturbances, a	**Bacteria**: *E. coli, Klebsiella* spp., *Enterobacter* spp., *P. aeruginosa, Serratia* spp., *C. freundii, M. morgagnii* **Resistant to**: not reported **Mechanism of resistance**: not reported	**Intervention** Norfloxacin 400 mg x2/day, minimum treatment seven days. *N*=52 (46 evaluable patients) **Control group** Aminoglycosides alone; aminoglycosides and meziocillin/ticarcillin; aminoglycosides and cephalosporin; aminoglycosides and vancomycin, cephalosporin, cefotaxime alone, administered in accordance with the manufacturers' guidelines. *N*=52 (48 evaluable patients) **Length of follow-up**: seven (SD two) days, optional four to six weeks	**Clinical success/improvement** 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 **Superinfection** Rates of superinfection and early re-infection also did not differ significantly between the norfloxacin and standard parenteral antibiotic treatment groups **Antibiotic resistance** No differences in the number of patients experiencing adverse events were found between those receiving norfloxacin and those receiving standard parenteral antibiotics	**RCT** Acceptable methodological quality (+)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	psychiatric disorder or central nervous system disease				
Giamarellou 1990 RCT **Setting** Tertiary (one ICU) Greece Dates not reported	To evaluate the efficacy of monotherapy with pefloxacin in secondary ICU pulmonary infections in comparison with imipenem **Participants** *N*=71 Adults 19–45 years, middle aged 46–64 years, aged 65–79 years, elderly 80+ years Male: 42, female: 29 Inclusion criteria: adult patients presenting serious bacterial infections of the respiratory tract Exclusion criteria: not reported	**Bacteria**: *E. coli, K. pneumoniae, Enterobacter* spp. (various Enterobacteriaceae), *P. aeruginosa, A. anitratus, P. mira, S. marcescens* **Resistant to**: aminoglycosides (gentamicine, tobramycin, netilmicin, amikacin), aztreonam, carbapenems (imipenem), cephalosporins (cefotaxime, ceftazidime, ceftriaxone), fluoroquinolones (ciprofloxacin) **Mechanism of resistance**: not reported	**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 **Clinical success/improvement** No differences were found in the number of patients cured, the number with superinfection that was cured, the number showing improvement and the number experiencing treatment failure. Bacterial eradication rates were significantly lower in the imipemem group [55.3% vs 82.9%, respectively (*P*<0.001)] **Antibiotic resistance** Resistance development among persisting strains was also significantly different (data not reported, *P*<0.05) **Adverse events** No systemic reactions or abnormal laboratory parameters were reported in either treatment group	**RCT** Acceptable methodological quality (+)
Huttner	To investigate if intestinal carriage of	**Bacteria**: *Enterobacter*	**Intervention**	**Clinical success/improvement**	**RCT**

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
2013 RCT **Setting** Secondary (all inpatient wards of a single hospital) Switzerland June 2009–June 2012	ESBL-E can be eradicated **Participants** *N*=58 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	spp. (ESBL-E) **Resistant to**: cefotaxime, cefotaxime/clavulanic acid, ceftazidime, ceftazidime/clavulanic acid, cefepime, cefepime/clavulanic acid **Mechanism of resistance**: ESBL	Colistin sulfate 50 mg (equivalent to 42 mg colistin base or 1.26 million units 4x/day) and neomycin sulfate (250 mg equivalent to 178 mg neomycin base 4xday) 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 **Control group** Placebo. *N*=27 **Length of follow-up**: 28 (SD seven) days	The rate of eradication of ESBL-E was significantly different between 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 RCT **Setting** Secondary (seven cystic fibrosis centres) USA	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	**Bacteria**: *P. aeruginosa* **Resistant to**: aminoglycosides, fluoroquinolones **Mechanism of resistance**: not reported	**Intervention** Biofilm testing: bioflim 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 **Control group**	**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

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
February 2007–October 2007	Male: 25, female: 14 Inclusion criteria: diagnosis of cystic fibrosis, history of persistent *P. aeruginosa* airway infection, clinical stability at the time of screening, ≥14 years with at least one prior course of intravenous antibiotics Exclusion criteria: sputum culture negative for *P. aeruginosa*, sputum culture positive for *B. cepacia* complex species, hospitalization or treatment for an acute pulmonary exacerbation, treatment with oral or inhaled antipseudomonal antibiotics, or azithromycin or other macrolides, within 14 days prior to screening		Conventional testing: conventional regimens of two 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. *N*=19 **Length of follow-up**: 14 days	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	
Rattanaumpawan 2010 RCT **Setting** Tertiary (one hospital) Thailand July 2006–September 2009	To determine whether nebulized CMS as adjunctive therapy of Gram-negative VAP was safe and beneficial **Participants** *N*=100 Middle aged 46–64 years, aged 65–79 years, elderly 80+ years Male: 64, female: 36 Inclusion criteria: hospitalized patients, ≥18 years of age, diagnosis of Gram-negative VAP Exclusion criteria: not reported	**Bacteria**: *E. coli* (ESBL +ve) and *E. coli* (ESBL -ve), *K. pneumoniae* (ESBL +ve) and *K. pneumoniae* (ESBL -ve), *E. cloacae, P. aeruginosa, A. baumannii* **Resistant to**: aminoglycosides, carbapenems, fluoroquinolones **Mechanism of resistance**: ESBL	**Intervention** 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). *N*=51 **Control group** 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	**Mortality** Rates of mortality due to VAP and all-cause mortality did not differ between the groups receiving intervention or control **Clinical success/improvement** 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 The overall incidence of complications, bronchospasm and	**RCT** Acceptable methodological quality (+)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
			systemic antibiotic therapy of VAP was ended. *N*=49 **Length of follow-up**: 28 days	renal impairment did not differ between the two treatment groups	
Stenderup 1983 RCT **Setting** Community Denmark Dates not reported	To study the use of mecillinam as a prophylactic for travellers' diarrhoea **Participants** *N*=74 tourists Adults 19–45 years, middle aged 46–64 years, aged 65–79 years, elderly 80+ years Male: not reported, female: not reported Inclusion criteria: Danish tourists travelling to Egypt and the Far East Exclusion criteria: not reported	**Bacteria**: Enterotoxogeni *E. coli* **Resistant to**: mecillinam, tetracyline, sulfonamide, streptomycin, chloramphenicol, kanamycin, ampicillin, cephalosporin, carbenicillin **Mechanism of resistance**: not reported	**Intervention** Mecillincam, 200 g, 1x per day for 25 days. *N*=38 **Control group** Placebo. *N*=36 **Length of follow-up**: duration of treatment	**Antibiotic resistance** Only 8% of *E. coli* 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 *E. coli* was resistant to more than three antibiotics	**RCT** Low methodological quality (0)
Tannock 2011 RCT **Setting** Primary (14 long-term care facilities) New Zealand Dates not reported	To test the efficacy of probiotic strain *E. coli* Nissle 1917 in reducing the carriage of MDR *E. coli* **Participants** *N*=70 Age: not reported Male: not reported, female: not reported Inclusion criteria: not reported Exclusion criteria: not reported	**Bacteria**: *E. coli* **Resistant to**: fluoroquinolones (norfloxacin) **Mechanism of resistance**: ESBL	**Intervention** Probiotic: strain *E. coli* Nissle 1917, $5x10^9$-$5x10^{10}$ CFU one capsule twice daily for five weeks. *N*=36 **Control group** Placebo starch powder capsule. *N*=33 **Length of follow-up**: five weeks	**Clinical success/improvement** 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. **Antibiotic resistance** 103 norfloxacin-resistant *E. coli* isolates from 20 probiotic patients were tested for susceptibility. All isolates were resistant to norfloxacin (MIC >256 µg/mL) and ciprofloxacin. The majority of norfloxacin-resistant *E. coli* isolates were MDR. The	**RCT** Acceptable methodological quality (+)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
				combination of MDRs differed among strains. None of the isolates were ESBL producers.	
Wang 2009 RCT **Setting** Tertiary (one ICU) China March 2006–July 2006	To report the effectiveness of extended-infusion meropenem compared with conventional bolus dosing in the management of HAP due to MDR *A. baumannii* **Participants** *N*=30 Adults 19–45 years, middle aged 46–64 years, aged 65–79 years Male: 19, female: 11 Inclusion criteria: HAP due to MDR *A. baumannii* Exclusion criteria: not reported	**Bacteria**: *A. baumanniii* **Resistant to**: carbapenems (meropenem) **Mechanism of resistance**: not reported	**Intervention** Extended intravenous meropenem infusion: 500 mg every 6 h over a 3-h infusion. *N*=15 **Control group** Conventional treatment: intravenous meropenem 1 g. every 8 h over a 1-h infusion. *N*=15 **Length of follow-up**: duration of treatment	**Clinical success/improvement** 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 **Antibiotic resistance** No patient developed a meropenem-resistant strain of *A. baumannii*, and the MIC_{90} for meropenem against *A. baumannii* remained at 2 µg/mL	**RCT** Acceptable methodological quality (+) Small sample size
Xue 2009 RCT **Setting** Tertiary (one ICU) China June 2007–December 2007	To determine the relation of carbapenem restriction with the incidence of MDR *A. baumannii* in VAP **Participants** *N*=26 Adults 19–45 years, middle aged 46–64 years, aged 65–79 years Male: 15, female: 11 Inclusion criteria: patients receiving mechanical ventilation for more than five days and diagnosed with VAP	**Bacteria**: *A. baumanniii* **Resistant to**: carbapenems **Mechanism of resistance**: ESBL	**Intervention** 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. *N*=12 **Control group** Conventional treatment: no restrictions of carbapenem (doctors were able to prescribe if necessary). *N*=15	**Mortality** The rates of mortality did not differ significantly between the treatment groups (RR 0.78; 95% CI 0.29–2.12). **Antibiotic resistance** More patients in the conventional group developed a carbapenem-resistant strain of *A. baumannii*, although the difference was not statistically significant (RR 0.63; 95% CI 0.38–1.04)	**RCT** Low methodological quality (0) Small sample size

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	Exclusion criteria: not reported		**Length of follow-up**: duration of treatment		

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.

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Appendix D. Excluded clinical studies

Study design

Case–control study

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Appendix E. Peer review

Healthcare Infection Society

Consultation – Joint Working Party on multi-drug resistant Gram-negative infections: prevention and control

Closing date: 5pm 31st October 2014

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Please note: comments will only be accepted electronically on this proforma.	

Please provide comments on the draft guideline on the form below, putting each new comment in a new row. When feeding back, please note the section you are commenting on (for example, Section 1 Introduction and line number). If your comment relates to the guideline as a whole, please put ‘general’. Add extra rows if required.

Section	Comments	
Line 256	Delete word ‘in’	Amended
Line 315	Amended	Amended
Line 318	I don't think this is necessary and could give false assurance. See Scottish Guidance Version 2.0 July 2014. Guidance for neonatal units, adult and paediatric intensive care units in Scotland to minimise the risk of *Pseudomonas aeruginosa* infection from water. Page 10 ‘Routine sampling of water to detect *Pseudomonas aeruginosa* should not be carried out.’	Sentence
Line 324	Do you mean ‘selective decontamination of the digestive tract’?	Amended
Line 327	What is this?	Amended
Line 330	.....and nursing staff	Amended
Line 334	Why is this percentage sign at the end of the lines?	Amended

Closing date: Please forward this electronically by 5pm on 31st October 2014 at the very latest to consultations@his.org.uk

Healthcare Infection Society

Consultation – Joint Working Party on multi-drug-resistant Gram-negative infections: prevention and control

Closing date: 5pm 31st October 2014

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Please note: comments will only be accepted electronically on this proforma.	

Please provide comments on the draft guideline on the form below, putting each new comment in a new row. When feeding back, please note the section you are commenting on (for example, Section 1 Introduction and line number). If your comment relates to the guideline as a whole, please put ‘general’. Add extra rows if required.

Section	Comments	
Line 256	Remove word ‘in’	Amended
Line 292 and line 1501	Why gowns instead of aprons?	Amended
Line 297	Isolate those colonized. This can prove extremely difficult due to pressures for single rooms.	Amended
Line 310	ATP testing for monitoring the environment. Not widely used at present.	Amended
Line 320	Hydrogen peroxide vaporizers. Not many hospitals own these.	Not changed as hospitals can hire them
Line 688	Enterobacteriaceae. This word is repeated.	Amended

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Healthcare Infection Society

Consultation – Joint Working Party on multi-drug-resistant Gram-negative infections: prevention and control

Closing date: 5pm 31st October 2014

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Section	Comments	
General	The document presents a very thorough and systematic review of current evidence in the area of prevention and control of MDR Gram-negatives and provides the strength of the evidence and associated recommendations. It provides a solid basis for the development of guidance in this area. The initial review of the current epidemiology of a range of MDR Gram-negative organisms is also very helpful.	
Page 25	In the Recommendation: 'Screening for carbapenem-resistant organisms should be prioritized to patients admitted from ICU and from post-acute facilities' – please clarify if post-acute facilities includes long-term care facilities, and if this recommendation refers to all admissions to any ward from post-acute facilities.	Amended
Page 50	A Vietnamese study on patient isolation is mentioned (Schultsz, 2013) – but in the second sentence, it is stated that the study did not include patient isolation. Please clarify.	Amended

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Healthcare Infection Society

Consultation – Joint Working Party on multi-drug-resistant Gram-negative infections: prevention and control

Closing date: 5pm 31st October 2014

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Section	**Comments**
General	Well-designed and presented review of the evidence. Will have significant implications for practice in terms of screening and isolation as expected.

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Healthcare Infection Society

Consultation – Joint Working Party on multi-drug-resistant Gram-negative infections: prevention and control

Closing date: 5pm 31st October 2014

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Section	**Comments**
	Very comprehensive document

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Healthcare Infection Society

Consultation – Joint Working Party on multi-drug-resistant Gram-negative infections: prevention and control

Closing date: 5pm 31st October 2014

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Section	Comments	
HIS comments	The following are a summary of comments received from those who have responded through HIS. All those who submitted comments were highly appreciative of the guidelines in general and welcomed their imminent appearance. Also recognized the huge amount of work undertaken. The guidance is welcomed as a substantial improvement on the PHE guidance 'CPE Toolkit.	
General comments	1. As someone trained on a diet of concern about gentamicin resistance, it concerns me greatly that there is no mention of aminoglycoside resistance in this document. Even quinolone resistance gets a brief mention but other than that, it is all carbapenemase, ESBLs, AmpC and Acinetobacters. If aminoglycoside resistance is no longer a concern, you should at least state why. Meanwhile, here on the ground, we will just monitor its inexorable rise in these days of avoiding broader spectrum agents! 2. Standard infection control precautions, measures, standard precautions – too many terms. Use one and define please. 3. The term 'high-risk patients' is used often in the document. Sometimes loosely. Is it high risk of having or acquiring CPE?	D. Livermore added text Amended Defined in glossary
Section 4 Summary of Guidelines	The term 'post-acute care' is not a commonly used term and is ambiguous. When I read the recommendation in the summary at the beginning, I took it to mean 'admission from acute care elsewhere'. It was only on reading the body of the text that I see that you mean admission from rehab, nursing and	Amended

Section	Comments	
	residential facilities. Please clarify.	
	Line 343 Not just decontaminating respiratory equipment in handwash stations (not wash basin), it is not tipping respiratory secretions or ventilator exudates into handwash stations – these are to be used for handwashing only. See relevant Chief Executive Letters, Health Protection Scotland.	Amended
	Line 492 The terms ‘plasmid outbreaks’ and ‘plasmid-related outbreaks’ are both used – please use one.	Amended
	Line 647 There is a notable seasonality to all Gram-negative bacteraemias – which season?	Amended
	Line 704 For ESBL carriers.... is a risk factor for what – infection or colonization or both?	Amended
	Line 785 Needs a line after surveillance ‘of what to detect what’.	Heading amended
Section 7.3.1 Testing of diagnostic samples	Line 840 Whilst recognizing the lack of specificity, is ertapenem a more convenient screening test for widespread screening for urine Enterobacteriaceae isolates than testing meropenem and cefpodoxime?	Not changed as counter to
	Line 870–871 Which means what for the UK?	Amended
	Line 891 Note no limit of time here, no risk assessment of degree of exposure or amount of organism on the patient. Are we sure?	Amended
Section 7.3.3 How should we undertake local surveillance, why is it important and how should it be interpreted?	Line 940 ‘Passive surveillance is not recommended when outbreaks are anticipated and clinical risk is high.’ This recommendation doesn't make sense. Even after reading the section, I'm unclear as to what is being recommended — except when outbreaks are anticipated, or not at all?	Amended

Section	Comments	
Section 7.4.2.2 What organisms should screening include?	Line 1130 This is too non-specific re: *Pseudomonas* are often resistant to carbapenems and I would not want to necessarily be chasing these – perhaps specify VIM/IMP-resistant strains.	
Section 7.4.2.3.1 Whom to screen	Line 1134 Until such times as PHE are prepared to allow us mere mortals on the front line access to up-to-date UK epidemiology, there is no point in recommending screening from UK institutions with a high prevalence (line 1163). How about an additional recommendation to make UK epidemiology available to us all?	Probably outside remit
Section 7.4.3.2 Disposable aprons and gloves	Line 1501 Comment: The evidence supplied does not suggest gowns over aprons, although from a practical perspective, gowns may be preferable on occasions (close body contact with patient), but are we suggesting entering the room wearing gowns?	Changed all to say apron
Section 7.4.2.1 What is the role of screening in patients and staff?	Line 1084–1091 You provide no evidence to back up the statement that cross-transmission is by members of staff via hands with the statements below. In fact, the evidence presented in this paragraph does not support the assertion.	Sentence deleted
	Line 1093 Does not make sense..... This has to be combined with the full implementation of standard infection control precautions throughout the care area.	Amended
Section 7.4.2.3.2 How to screen	Line 1179 In practice, staff don't like doing rectal swabs and patients don't like having them done. We find that if it is possible to visualize faeces on the swab, then you don't have long to wait for a stool sample so why not just request a swab from a stool sample unless in an outbreak situation. Don't request a stool sample or it will inevitable get diverted to the stool bench.	Amended
Section 7.4.5.1 When should the environment be	Line 1742 Comment: There is not enough guidance about how to screen and the sensitivity of screening. I would say ‘consider screening’.	Amended recommendatio

Section	Comments	
sampled?		
	Line 1742 Comment: It doesn't seem to me that the evidence supplied suggests this is 'strong' evidence outside of *Acinetobacter* spp. The major problem at present is carbapenemase-producing Enterobacteriaceae rather than *Acinetobacter* spp., and to place great relevance on environmental screening is not correct or helpful practically.	As above
Section 7.4.2.4 What can be done in the case of patients unable or unwilling to consent to a rectal swab?	Line 1287 and further lines elsewhere. If they are in isolation, transmission-based precautions are being used. Everyone is applying SICPs for all patients all of the time.	Amended
Section 7.4.2.6 Is there evidence for effective interventions on positive patients i.e. can they be cleared?	Line 1345 YOU NEVER DISCONTINUE SICP! This paragraph needs rewriting.	Contact precautions introd

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Healthcare Infection Society

Consultation – Joint Working Party on multi-drug resistant Gram-negative infections: prevention and control

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Section	Comments	
General	MRSA Action UK welcomes this guidance. We would like to see a plain English guide for patients with leaflets and publicity to raise awareness of this important and significant issue. There is patient acceptability with regard to MRSA screening in most instances, and this is largely attributable to the well-publicised information on MRSA and the interventions that have been put in place to prevent it. Information about the need to diagnose MDR Gram-negative bacteria in high risk patients and the measures needed to deal with it should, we believe, be well publicised.	Leaflets are planned
Summary of guidelines Line 301	Establish a robust flagging system for patient notes. Change ‘weak’ to ‘strong’. Rationale: Information on carriage or infection is important, particularly when transferring patients between facilities. This information is essential in identifying high-risk patients for screening.	Weak relates to the stren
Summary of guidelines Line 328–329	In areas where numbers justify, consider a separate dedicated nursing unit and monitoring hand hygiene of shared medical staff. Change ‘weak’ to ‘strong’. Rationale: Monitoring of hand hygiene of medical staff at the point of care is important, particularly in an outbreak with	

Section	Comments	
	these significant bacteria. This matches the ‘strong’ recommendation ‘To prevent any hospital-acquired infection, hand hygiene is required before and after direct patient contact, after contact with body fluids, mucous membranes and non-intact skin, after contact with the immediate patient environment and immediately after the removal of gloves.’ in line 302–305.	

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Healthcare Infection Society

Consultation – Joint Working Party on multi-drug-resistant Gram-negative infections: prevention and control

Closing date: 5pm 31st October 2014

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Section	**Comments**	
General comments	With the current focus on carbapenemase-producing Enterobacteriaceae and, given this guidance includes other MDR organisms (e.g. ESBL, AmpC producers), it will be important to emphasize that prevention of transmission for any of these organisms should be paramount. In relation to lay/patient representation, it may be that the lay summary would sit better below the executive summary. An introductory statement would help to set the context, describing what the report sets out to do and group representatives, including patient representatives. Sentence two of the summary could be clearer. The words bacteraemia/bacteremia and colonised/colonized have been used	Amended

Section	Comments	
	interchangeably throughout. Generally, recommendations need to be more prescriptive and consistent with that highlighted in the narrative.	Corrected
Specific line comments		
Section 4: Line 326**:** Code of Practice HPA 2013	Should this be the Code of Practice which is part of the Health and Social Care Act or the HPA/DH 'Prevention and control of infection in care homes – an information resource'?	HPA 2013 but as va
Section 5: Line 335: Audit measure 'All patients infected with meropenem-resistant Gram-negative bacteria to be reported to Public Health England or equivalent bodies'	It is unclear whether this should include colonization; reporting to PHE centres or equivalent.	Amended
Section 7: Line 423: *'…*healthcare-acquired infections often become apparent after hospital discharge'	It should be noted that healthcare -acquired infections could denote health care in a hospital or the community – it is assumed hospital-acquired infection is what is implied.	Amended
Line 434 '…can persist for much longer periods (commonly up to a year), and we recommend that this longer period be used'	In assessing community vs hospital-acquired infection, it is not clear, by considering hospitalization in the last year, whether this will elucidate place of acquisition (considering the difficulty determining chronology) in revolving door patients; it would be useful to reference this.	Referenced

Section	Comments	
Section 7.1.4.2 Line 495: ‘This is found, for example, in the current spread of pKpQIL plasmids encoding KPC carbapenemases in and around Manchester.’	This is a working assumption but is not proven.	Amended
7.1.4.4 Line 531 ‘Long-term care facilities range from establishments offering assisted-living to largely independent residents through to those providing complex medical support (CDC 2014, Lievesley 2011)’	Do you mean the Centre for Policy on Ageing rather than CDC?	CDC is correct
Section 7.1.5 Line 604 ‘ numbers’	Typographical error.	Corrected
Section 7.2 Line 682 Recommendation; ‘Screening for carbapenem-resistant organisms should be prioritized to patients admitted to ICU and from post-acute care facilities.’	The evidence does not directly support this recommendation. The key issue is whether we are trying to prevent infection (and thus focus on critical care may be appropriate) or transmission (and thus we need to target all at-risk patients). This is inconsistent with the Acute Toolkit. In Greater Manchester, risk is more associated with previous hospital admissions than post-acute care facilities.	Amended
Section 7.2.1 Line 688 Enterobacteriaceae repeated	Typographical error.	Corrected
Line 694 ‘…common environmental sources have occasionally been described and should be sought where no other plausible vectors can be found’	It is unclear what this means without identifying common sources/supporting with evidence.	Amended
Section 7.2.1 Line 711–716 ‘Screening for carriers with subsequent isolation of those identified is effective in preventing transmission and is important for early recognition of individuals at high risk of carriage of carbapenem-resistant Enterobacteriaceae	Should there be recommendations associated with this statement?	Background informa

Section	Comments	
Awareness of carriage is important and, therefore, communications regarding patients who are known to be infected or colonized with MDR strains is essential when transferring patients within and between institutions.'		
Section 7.3.2 Line 876–877 Recommendation Antimicrobial susceptibility data on all routine isolates should be reported electronically to a central national database, preferably from all body sites.	It would be useful to have a recommendation about outputs of recommended surveillance in addition to inputs. The guidance makes recommendations for reporting of sensitivities on all significant isolates to PHE, but makes no comments on what output is required. Analysis of data by acute trust is required. Mandatory reporting is an approach supported by some as a way of ensuring that all trusts report.	Amended
Section 7.3.3 Line 880–881 How should we undertake local surveillance, why is it important and how should it be interpreted?	It would be helpful to clarify what is meant by local – is this trust/laboratory level, or local authority level?	Amended
Line 882: 'Where warranted to track resistance types (e.g. carbapenemase producers), local screening should be performed'	Is this the only reason for screening? It will also inform and evaluate infection prevention and control practices.	Amended
Line 886: '…it is critical to ensure the compliance of staff taking the samples by means of audit and feedback'	It is not clear whether this means compliance with guidance indicating when to take samples or how to take samples or other.	Amended
Line 898–899 Local surveillance provides more rapid notification of an emergent problem than the	The reference laboratory does not actually undertake surveillance. A definition of local surveillance is required. The presumption is that this is trust level	Amended

Section	Comments	
reference laboratory surveillance, particularly if a single clone and species is responsible	surveillance.	
Line 910–913: Screening on admission and weekly until discharge should be performed on patients at risk, known to be colonized or their nearby contacts as part of a package of measures to control an outbreak	If a patient is known to be colonized on admission, it is unclear why they should be screened on admission. The meaning of the wording 'known to be colonized or their nearby contacts' is unclear.	Amended
Section 7.3.4 Line 926	Appears to have lost text as next sentence appears to be a 'follow-on' rather than the start of a topic.	Amended
Line 939 Recommendation: 'Passive surveillance is not recommended when outbreaks are anticipated and clinical risk is high'	It is unclear what is meant by 'when outbreaks are anticipated'; by their very nature, outbreaks are not expected.	Amended
Section 7.4.1: Line 966–967: '…of hospital patients without the clear identification of such movements to the laboratory'	This line appears muddled/misplaced.	Amended
Line 986: 'Public Health England, Centers for Disease Control, ESCMID all recommend contact precautions...'	PHE toolkit recommends standard precautions not contact precautions.	Amended
Line 993: 'emphases…'	Typographical error.	Amended
Section 7.4.1 Line 1030–1031 'Assess all patients for infection risk on arrival at the care area (if possible, prior to accepting a patient from another healthcare area) and continuously review patient infection status throughout their stay.'	Infection risk or colonization risk? Or should it be transmission risk?	Amended

Section	Comments	
Line 1039–1040 Do not discard body fluids, secretions or exudates into handwash basins	Should this also include water used to wash patients or the environment?	Amended
Section 7.4.2 Line 1103: ‘Screening of potential carriage sites in patients should be undertaken as part of a package of infection control measures for carbapenemase-producing Enterobacteriaceae to prevent the spread of outbreak strains’	This should clarify which patients.	At risk, addressed la
Line 1169 ‘Given the likelihood of prolonged gastrointestinal carriage of MDR Gram-negative organisms, clearance samples are not recommended’	As this is termed as ‘likelihood’ rather than clearly evidenced, would clearance samples provide valuable information about the patient’s status at the same time as increasing our knowledge about carriage duration?	Amended. The table
Section 7.4.2.3.3 Line 1266 ‘Effective communications between healthcare settings will help facilitate efficient patient transfers’	As this is a crucial measure in reducing spread, could a recommendation be associated with this?	Amended
Section 7.4.2.4 Line 1272 ‘In situations where a patient is incapacitated and cannot sign, it may be considered permissible for those giving care to proceed with any interventions’	Suggest strengthen from ‘may be permissible’ to ‘those giving care may proceed’.	Amended
Line 1281: ‘Patients should be informed, whenever possible, of the need and reason for screening (i.e. that it is for their benefit …)’	To some extent, this is contradictory to line 882 re tracking resistance types.	No change

Section	Comments	
Line 1283: ‘They should be given the option of who carries it out, including self-screening if the patient is able and prefers it’	Depending on the patient, self-screening with a rectal swab may not be safe or realistic.	Amended
Section 7.4.2.6 Line 1345: ‘SICP’	This needs to be spelled out.	Amended
Line 1348: ‘…organizations should be cautious in discontinuing contact precautions’	Advice appears to switch between standard and contact precautions.	Amended
Line 1377–1379 ‘Local screening policies should be developed to define those patients at high risk of carriage of, for example, carbapenemase producers. All patients transferred from healthcare facilities with endemic carbapenemase-producing Enterobacteriaceae at home or abroad should be screened’	Consider adding ‘or with a history of admission to’.	Amended
Line 1386–1387 Patients colonized with carbapenem-resistant organisms should be isolated for the duration of their stay where possible	It needs to be clear what the implications are for future stays.	Amended
Section 7.4.5.3 Line 1835 ‘Water sources should be sampled at least twice a year for *P. aeruginosa* in augmented care units and point-of-use filters installed or taps changed when levels of patient colonization or infections rise.’	The group recommend twice-yearly testing of water in augmented care units for *Pseudomonas* spp. This is in line with national guidelines, but it is even more important to stress the requirement for a full risk assessment in relation to these guidelines. For example, removal of automatic taps, removal of thermostatic mixing valves, removal of flow straighteners, design of sinks etc. The Health Technical Memorandum does not specifically advise frequency of testing. There is no evidence to support twice-yearly testing.	Amended

Section	Comments	
	The group recommend the use of filters. These may be of short-term use whilst engineering solutions are implemented, but the *Pseudomonas* advisory group also found evidence that the filters themselves can become a source of *Pseudomonas* spp. because of where they are fitted. There is also some evidence that these filters actually deflect the *Pseudomonas* spp. (and *Legionella* spp.) to other parts of the pipework. Further data can be obtained from the PHE team at Porton Down.	
Table 4: 'Carbapenem-resistant Enterobacteriaceae – screen all patient contacts in ward of case who has not been identified and isolated'	Advice in the table in areas such as this are confusing/do not make sense.	Amended

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Healthcare Infection Society

Consultation – Joint Working Party on multi-drug-resistant Gram-negative infections: prevention and control

Closing date: 5pm 31st October 2014

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Section	Comments	
Numerous (1)	There are a number of confusing references to terms to describe different levels of IPC precautions; when discussing managing cases, the terms ‘isolation’, ‘contact precautions’ and on one occasion at least ‘standard infection control precautions’ are used seemingly interchangeably. The guidance also refers to long-sleeved gowns without a discussion (as these do not routinely form part of contact precautions, a discussion is merited). Examples given below (some not all, there are many).	Amended
Numerous (2)	There are a number of England only references to regulation and regulatory structures – is this an England only document? Examples given below.	Amended
Section 7.3.4	When are the situations when outbreaks can be ‘anticipated’?	Amended
Section 7.4.2.4	Example of IPC precautions terminology: ‘ isolation with standard infection control precautions’.	Amended
Section 7.4.2.6	As above: ‘..criteria for discontinuing SICP...’ (SICP should never be discontinued).	Amended
‘ ‘	As above: it then goes on to refer to contact precautions.	Amended
‘ ‘	As above: term used is isolated (nothing wrong with that but no consistency of language).	Amended
Section 7.4.5.4	Example of England only: the NHS constitution is England only I believe.	Amended
Section 7.5	As above: the Code of Practice and Care Quality Commission are England only.	Amended
‘ ‘	As above: the recommendation is England only.	Amended

Section	Comments	

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Healthcare Infection Society

Consultation – Joint Working Party on multi-drug-resistant Gram-negative infections: prevention and control

Closing date: 5pm 31st October 2014

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Section	**Comments**	
Section 4 Line 253–255	'Screening on admission and weekly until discharge should be performed on patients at risk, known to be colonized or their nearby contacts as part of a package of measures to control an outbreak' Please could it be clarified with the working group as to what the goal of screening patients known to be colonized with MDR Gram negatives is. The use of screening with regards to contacts and those at risk is clear; however, we would view patients known to be colonized as colonized and isolate them and take infection control precautions for them as a matter of course. As we have no method of decolonizing them, and the sensitivity of the screening test is not absolute, we would not view a negative result as one that would allow us to relax precautions. If the guidance pertains to trying to get specimens to link them to a potential outbreak, I can see the use in this, but otherwise screening known carriers will likely utilize resources to generate results that do not alter management.	Amended
Section 4 Line 256–257 and Section 7.3 Line 940–941	'Passive surveillance is not recommended in when outbreaks are anticipated and clinical risk is high' 'in when' is likely a typo	Amended
Section 7.18 Line 682–683	'Screening for carbapenem-resistant organisms should be prioritized to patients admitted to ICU and from post-acute care facilities' Please could it be clarified if it is recommended that all patients admitted to ICU and from post-acute care facilities should be screened, and if so, whether they should all be screened weekly until discharge. I found this	Amended

Section	Comments	
	a bit unclear.	
Section 7.3 Line 874–875	‘Laboratories should test meropenem susceptibility in all clinically significant Gram-negative isolates if possible and blood isolates as a minimum’ It lies beyond the capacity of many laboratories to test meropenem in all Gram-negative isolates, especially urine cultures and sputum cultures which are high volume and where the significance is not always known. It might be better to focus this on resistant organisms or potentially on sterile site cultures. I do appreciate though that it is aspirational and only says blood cultures as a minimum.	Amended – currently

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Section	**Comments**	
Page 15 Line 397	ESCMID, not ECCMID	Amended
Page 17 Line 448	Diarrhoea and incontinence maybe	Amended
Page 29 Line 813	Please allow us to ask why not use ertapenem as a first-step screening to detect carbapenemases, as it is the most sensitive carbapenem	Amended
Page 51 Line 1501	We would like to point out that glove use is not advised systematically by some national infection control societies (e.g. France), as it is associated with decreased hand hygiene	Noted

Section	Comments	
Page 54, Line 1616	In Section 7.4.4, we would suggest to reconsider ‘equality of liquid soap and water WITH alcoholic hand rub’, we think alcoholic hand disinfection should rather be favoured and handwashing be restricted to visibly soiled hands only (otherwise it may be confusing/unclear and could be inefficient in breaking the chain of transmission of all Gram-negative bacteria).	Amended
Section 7.4.5	Environmental cleaning could address surface disinfection techniques of the surfaces adjacent to the patient and sanitary cell.	Discussed later
General	May we suggest to add a section/subsection about reprocessing bed pans (automated bedpan reprocessing is a crucial issue for at least all MDR Enterobacteriaceae and *Pseudomonas* spp.) and maybe also about reprocessing flexible colonoscopies.	Query added to text
General	Clarification of the specific organisms: the ESCMID guidelines and the point about ESBL *E. coli* not to target anymore is mentioned, but we do not see this mirrored in the recommendation; we would suggest that for ESBL *E. coli* standard precautions are sufficient except there is evidence for a so-called high-risk clone/superspreader of ESBL *E. coli* in an institution or within a region; in addition, the high potential of transmission of *Klebsiella* spp. (ESBL + KPC) may be stressed more strongly.	Sentence added
General	We would like to suggest to harmonize the definition of ‘multi-drug-resistant’ with the one recommended internationally by ECDC and CDC, amongst others (Magiorakos, Clinical Microbiology & Infection).	Definition kept consi
General	Can we suggest that detection of ESBL producers focuses on *K. pneumoniae*, *Enterobacter* spp., *Serratia* spp. (and not *E. coli*). Tacconelli E, Cataldo MA, Dancer SJ, *et al*.; European Society of Clinical Microbiology. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. *Clin Microbiol Infect* 2014;**20**(Suppl. 1):1–55.	Amended
General	ESGARS: The use of rapid diagnostic tests for ESBL and carbapenemases (Carba NP, ESBL NDP, MALDI-TOF application) may be considered.	Added for considera

Section	Comments	
	Nordmann P, Poirel L. The difficult-to-control spread of carbapenemase producers among Enterobacteriaceae worldwide. *Clin Microbiol Infect* 2014;**20**:821–830. Burckhardt I, Zimmermann S. Using matrix-assisted laser desorption ionization-time of flight mass spectrometry to detect carbapenem resistance within 1 to 2.5 hours. *J Clin Microbiol* 2011;**49**:3321–3324. Nordmann P, Poirel L, Dortet L. Rapid detection of carbapenemase-producing Enterobacteriaceae. *Emerg Infect Dis* 2012;**18**:1503–1507. Nordmann P, Dortet L, Poirel L. Rapid detection of extended-spectrum-β-lactamase-producing Enterobacteriaceae. *J Clin Microbiol* 2012;**50**:3016–3022.	

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Healthcare Infection Society

Consultation – Joint Working Party on multi-drug-resistant Gram-negative infections: prevention and control

Closing date: 5pm 31st October 2014

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Please note: comments will only be accepted electronically on this proforma.	

Please provide comments on the draft guideline on the form below, putting each new comment in a new row. When feeding back, please note the section you are commenting on (for example, Section 1 Introduction and line number). If your comment relates to the guideline as a whole, please put ‘general’. Add extra rows if required.

Section	Comments	
General	The recommendations for different MDR Gram-negative bacteria need to be separated because the infection control precautions for ESBLs, *Pseudomonas* spp. and carbapenamase-resistant organisms are very different. Combining them make the document confusing and it is difficult to easily see what precautions are relevant for different MDR Gram-negative bacteria.	Amended
General	Not all the recommendations are clearly mapped to the evidence presented, and it is therefore difficult to see how or why they are justified. Table IV would be improved by separating out the different organisms (see Point 1) and indicting the grade of evidence – not clear why this is there for the pseudomonas column but not the others.	Amended
General	The critical appraisal of evidence derived from outbreak studies or other poor-quality studies is minimal and there is a danger that what is presented reflects 'opinion' rather than robust evidence. Whilst the former may be reasonable, it is important to distinguish where recommendations are based on high-quality evidence and give some indication of the, often strong, biases evident in outbreak studies. Where the recommendation is based on expert opinion, the measure of certainty that they are effective and balance between desirable/undesirable effects should be clear.	Amended
General	Maybe it is intended to include as an appendix, but it would be helpful to see the evidence tables to understand how the recommendations have been supported by evidence. As many of the studies included are outbreak, it is difficult to see how these could be described as 2+. Many other recommendations including strong recommendations are not linked to a level of evidence.	Amended. The systematic review found only
General	GRADE recommends that recommendations are 'specific' and 'actionable'; not all of those included meet these criteria. GRADE is not advised for use with 'good practice recommendations' may be the problem with the approach taken here. It is also not advised to attempt to grade obvious procedures or standard practice. The list of	Amended

Section	Comments	
	recommendations may be easier to follow if they are divided by subheadings into areas of practice, e.g. screening, infection control procedures, management of outbreaks etc., and main groups of MDR Gram-negative bacteria.	
General	Previous high-quality evidence reviews should have been used to either support recommendations or to refer to, rather than attempt to undertake a superficial review that comes up with incomplete recommendations. In particular, this relates to aspects of practice covered by EPIC 3 (Loveday *et al*., 2014) and by the systematic review of *Pseudomonas* spp. in healthcare water systems (Loveday *et al.,* 2014).	Amended
General	The terminology of 'screening', active and passive surveillance is confusing and the terms seem to be used interchangeably.	Amended
General	Target audience should be clarified. One mention of care homes at end of document – rest not relevant to this setting and care home guidance is not detailed.	Disagree care homes mentioned several tim
General	There are a number of confusing references to different levels of IPC precautions; when discussing managing cases, the terms 'isolation', 'contact precautions' and on one occasion at least 'standard infection control precautions' are used seemingly interchangeably. The guidance also refers to long-sleeved gowns without a discussion (as these do not routinely form part of contact precautions, a discussion is merited). Examples given below (some not all, there are many). NOTE: I have not checked the tables for this issue.	Removed long sleeve reference, rechecked
General	There are a number of England only references to regulation and regulatory structures – is this an England only document? Examples given below. NOTE: I have not checked the tables for this issue.	Amended

Section	Comments	
Line 227–232	There are costs associated with extended screening/surveillance, isolation and cohorting patients. This includes adverse effects to the patient of being put in prolonged isolation. The efficacy of some of the proposed measures is, at best, uncertain and therefore it cannot be assumed that the costs will be offset by reduced transmission.	Amended
Line 241	Does this mean you should or shouldn't screen these patients? It seems to conflict with Page 11 Line 253.	Amended
Line 248	This is not a statement based on evidence; more a desired practice.	Removed
Line 251	What travel information and why/what should be done with it?	Amended
Line 256	This doesn't make sense and anyway is a double negative which in combination with a 'weak' recommendation makes it difficult to understand what the requirement is.	Amended
Line 258	This is not specific. Assess infection risk against what standards? What does 'infection status' mean and what action would be taken if it changed? Does it mean any infection or an MDR Gram-negative bacteria infection?	Amended
Line 261	Not specific.	Amended
Line 263, 265	These would be better cited as good practice recommendations and referenced to EPIC 3 which fully reviewed the evidence underpinning them.	Changed
Line 267	Whilst this may be 'guidance', it is based on extremely skimpy evidence. Again, suggest it should be listed as a good practice recommendation.	Disagree this is evidence based but moved
Line 269	This is not specific or actionable. What all patients? Which body sites? What package of measures? How is an outbreak strain defined?	Amended

Section	Comments	
Line 272	Not specific or actionable. Either screening is recommended or it is not. If it is going to be a recommendation, it should be 'preferred', preferred to what?	Amended
Line 282	This is two separate recommendations, although actually the first one is more of a 'good practice'.	Split
Line 286	Not specific or actionable. What does vigorously reinforced mean?	Amended
Line 289	Says the same thing twice.	Amended
Line 291	Why gowns? This is a very US approach. In the UK, we use aprons. There may be evidence that gowns might be necessary for abacters, but is there any evidence to suggest that they have a significant effect on transmission of other Gram-negative bacteria?	Gowns or aprons
Line 295	See earlier reference to EPIC 3.	Amended
Line 299	The priority is not just about MDR Gram-negative bacteria, the decision will depend on other infections too (*Clostridium difficile* infection, meticillin-resistant *Staphylococcus aureus*, tuberculosis etc.). Other recommendations are conflicting (i.e must isolate carbapenem-resistant Enterobacteriaceae but for ESBL isolate if possible). Cohort isolation should be a separate recommendation.	Amended. Not conflicting in that CRO highe
Line 303	See earlier reference to EPIC 3.	Amended
Line 307	Not specific.	Disagree
Line 310	There is no good evidence that monitoring based on ATP is effective in improving cleaning, and no evidence that it prevents transmission (which is presumably the outcome of interest for these recommendations).	Changed to 'weak'

Section	Comments	
Line 313	This is a good practice recommendation but actually should apply to any equipment, not just respiratory.	Amended
Line 315	What is the reason/evidence for this?	Removed as a recommendation
Line 317	This reflects (some of) the guidance on pseudomonas control – better to refer to other sources of guidance rather than partially repeat here. Evidence base is anyway minimal.	Amended
Line 320	What about cleaning with other disinfectants? There should be a more general recommendation – terminal cleaning after a case? Routinely for cleaning of area with infected patients? Or just for outbreaks? Is there evidence? Please note – there are costs associated with environmental damage of routine use of chlorine. It is frequently not feasible/practical to use H_2O_2 so important to recommend alternatives.	Added
Line 323	Think this means gut decontamination.	Amended
Line 325	Not specific – it is recommended for ICU patients to prevent VAP (and also for other patients at risk of HAP).	Removed
Line 326	Not specific or actionable.	Amended
Line 327	Is this for all patients or just those with MDR Gram-negative bacteria?	Amended
Line 329	Not specific or actionable. Monitoring hand hygiene a separate recommendation – why just medical staff?	Amended
Line 333	Isolates from blood cultures.	Amended
Line 334	What does significant Gram-negative isolates mean?	Amended

Section	Comments	
Line 335	This is not really an audit measure	Removed
Line 337	This is not really an audit measure	Removed
Line 343	This would be very difficult to audit	Removed
Line 441	References for this statement?	Referenced
Line 442	Vague and not referenced	Removed
Line 451	Are generally more likely to be associated with….	Amended
Line 505	References?	Not required
Line 511	Reference?	Added Villegas
Line 512–521	There is a comprehensive systematic review of evidence for risks and control of *P. aeruginosa* related to water systems (Loveday *et al*., 2014). Breathnach does not provide high-quality evidence (outbreak report), but there are others studies that provide better evidence to support control measure and risk factors.	Amended
Line 682	Does this mean you should or should not do it? Or should other patients be prioritized?	Amended
Line 700	This is fine but is not clearly reflected in the recommendations. Statement is not linked to evidence.	Deleted
Line 714	Reference?	Added
Line 748	What is the evidence for risk of resistance to chlorhex?	Amended
Line 759	There is no robust evidence to support this statement.	Amended

Section	Comments	
Line 760–767	This paragraph has not included critical appraisal of the evidence cited. See Loveday *et al.* for robust assessment of the quality of evidence of routes of transmission.	Added
Line 783	These are very old references.	Nil new
Line 871	Reference for this?	In section
Line 880	See previous comment about terms ‘screening/surveillance’.	Amended
Line 883	No such section.	Amended
Line 912	At risk of what?	Amended
Line 925	References?	Added
Line 940	When are the situations when outbreaks can be ‘anticipated’?	Removed
Line 987	Suggest define what is meant by contact precautions to avoid confusion and reference it (e.g. Seigel, 2007).	Amended
Line 1003	These refer to a combination of Seigel 2007 and EPIC (which does not include all these elements). Patient placement should be explained.	Referred to Siegel 2007
Line 1019–1021	Is this level of protection relevant to Gram-negative bacteria? If so, in which circumstances? Evidence/references?	Deleted
Line 1027	Discussion of the evidence suggests that contact precautions are required. These are different to the standard precautions recommended here. It may be necessary to recommend different things for different MDR Gram-negative bacteria.	Amended

Section	Comments	
Line 1030	These recommendations are not specific, especially in the absence of recommendations on how to decide whether a patient is an ‘infection risk’.	Amended
Line 1066	This refers to transmission-based precautions not contact precautions – which and when?	Amended
Line 1093	Not sure what this means. Low-grade evidence.	Amended
Line 1135	This implies screening of the majority of patients in hospital.	Amended
Line 1287	Example of IPC precautions terminology: ‘ isolation with standard infection control precautions’.	Removed
Line 1391–1400	There are no references or critical appraisal of evidence to support these statements or indication of situations where cohorting may be indicated. Conflicts with other statement about isolation not being practical for ESBLs. Example of IPC precautions terminology ‘...criteria for discontinuing SICP...’ (SICP should never be discontinued).	Amended
Line 1348	Example of IPC precautions terminology, it then goes on to refer to contact precautions.	Amended
Line 1386	Example of IPC precautions terminology, term used is isolated (nothing wrong with that but no consistency of language).	Amended
Line 1501	Why gowns? So is the advice to use contact precautions or standard precautions? It is not clear.	Amended
Line 1598	Conflicts with other evidence presented/recommendations that suggests isolation or ESBLs not practical. Evidence cited seems to be largely based on multiple interventions in outbreaks, therefore may not be very robust to support strong statement.	Amended

Section	Comments	
Line 1611	There are other much better source references of this evidence that can be cited. The general statement is not necessary for Gram-negative bacteria guidance.	Amended
Line 1726	Evidence for efficacy of ATP in preventing transmission is not sufficiently robust to support recommendations.	Changed to weak
Line 1737	The evidence for the efficacy of cleaning is systematically reviewed in EPIC 3. There is limited robust evidence. This section would be better focusing on strategies to ensure decontamination of the environment relevant to Gram-negative bacteria rather than sampling it.	There is already a decontamination section
Line 1752	Very-poor-quality evidence.	Amended
Line 1767–1776	See previous comments about review of evidence re *P. aeruginosa*.	Recommendation amended to include other
Line 1845	Example of England only: the NHS constitution is England only.	Added ‘In England’
Line 1916	Studies on H_2O_2 are not associated with low risk of bias (see EPIC 3). H_2O_2 may be a useful strategy for eliminating environmental reservoirs of MDR Gram-negative bacteria in some circumstances (e.g outbreaks of *Acinetobacter* spp.). Not sure there is sufficient evidence to say definitively it is effective in reducing environmental reservoirs.	Amended
Line 2002	The Code of Practice and Care Quality Commission are England only.	Amended
Line 2106	Source of this grading system not clear (previously referred to SIGN). Not clear how recommendations are linked to quality of evidence/balance between desirable/undesirable effects/values and preferences/costs as per GRADE.	Changed to updated 2014 SIGN system – s
Line 2109	Table IV good but needs heading on each page and best to have separate column for	Not changed

Section	Comments	
	ESBL/carbapenem-resistant Enterobacteriaceae throughout.	
Line 2024	The recommendation is England only.	Amended
Table	Not clear what 'other room or cohort' refers to. What are strict contact precautions?	Amended
Table	Why contact precautions when previously said standard precautions OK for ESBLs? Why soap and water? Why not alcohol hand gel?	Amended
Table	But what about respiratory equipment?	Amended
Table	Definition/evidence for increased cleaning frequency? What about other forms of environmental decontamination (e.g hypochlorite)?	New recommendation introduced
Table	Staff cohorting – extremely difficult, very costly and not relevant for ESBLs.	Agreed

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Please note: comments will only be accepted electronically on this proforma.	

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Section	Comments	
Section 7.3.4	Page 44 Line 1287 – describes SICPs – should this be 'transmission-based precautions (TBPs)' and again in line 1300. We should be using the same language as in the National Infection Prevention Control Manual.	Amended to single room, contact precautions, avoiding TBP as include droplet and airborne as well as contact
Section 7.4.2.6	Page 46 Line 1348 contact precautions – should be TBPs.	TBP include droplet and airborne, not implied here
Section 7.4.3.2	Page 50 Line 1469 Should read 'SICPs'.	Already there
Table 4	Page 81 Clinical practice – contact precautions should read TBPs, apron and gloves should read TBPs.	TBP include droplet and airborne, not implied here
Table 4	Page 83 Hydrogen peroxide – the recommendation in the literature for this is only weak. National Manual stipulates 'a combined detergent disinfectant solution at a dilution (1000 ppm av.cl.); (Actichlor plus)' there is no evidence within this document that this is not a sufficient method of cleaning. Page 63 Line 1892 notes that there are limited data on whether hydrogen peroxide reduces rates of acquisition. Not all boards will have access to hydrogen peroxide. If this is a method of cleaning that will be recommended, this should be included within the national manual. Otherwise, Actichlor plus is a system all boards are familiar with and currently use effectively to reduce cross-infection and in outbreak situations.	Amended to qualify use of fogging. Disinfectants are discussed in text
Table 4	Page 84 Staff cohorting recommended. Page 49 Line 1459 notes no studies have	Amended

Section	Comments	
	evaluated the impact of cohorting staff aside from other interventions. Staff numbers will not be sufficient to allow staff cohort with no evidence this is necessary. Why is this a recommendation? Staff education yes.	

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