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Guidelines

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

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1. Executive summary

Multi-drug-resistant (MDR) Gram-negative bacterial infections have become prevalent in some European countries. Moreover, increased use of broad-spectrum antimicrobial agents selects organisms with resistance and, by increasing their numbers, increases their chance of spread. This report describes measures that are clinically effective for preventing transmission when used by healthcare workers in acute and primary healthcare premises. Methods for systematic review 1946—2014 were in accordance with SIGN 50[1] and the Cochrane Collaboration;[2] critical appraisal was applied using AGREEII.[3] Accepted guidelines were used as part of the evidence base and to support expert consensus. Questions for review were derived from the Working Party Group, which included patient representatives in accordance with the Patient Intervention Comparison Outcome (PICO) process. Recommendations are made in the following areas: screening, diagnosis and infection control precautions including hand hygiene, single-room accommodation, and environmental screening and cleaning. Recommendations for specific organisms are given where there are species differences. Antibiotic stewardship is covered in a separate publication.

2. Lay summary

MDR Gram-negative bacteria are bacteria (or germs) that are resistant to at least three different antibiotics. These bacteria are commonly found in the gut, where they do no harm; however, they can cause infection at other body sites, mainly in patients who are vulnerable due to other underlying diseases, injury or hospitalization. Infection often happens when the bacteria enter the body through an open wound or via a medical device such as a catheter. Infections caused by MDR Gram-negative bacteria are difficult to treat, and can cause additional pain to patients with slow wound healing and other complications such as pneumonia or infection in the blood. This can prolong the length of stay in hospital and, in some cases, can cause death.

Some types of resistant Gram-negative bacteria can be carried on the skin rather than the gut, again with no obvious signs or symptoms. 'Colonization' describes this carriage of bacteria in the gut, on the skin or in the nose, throat or elsewhere on the body. Although the patients lack symptoms of infection, they may still need to be isolated/segregated and/or other contact precautions may be necessary in order to stop their resistant bacteria spreading to others.

3. Introduction

This guidance has been prepared by the Working Party to provide advice on screening (testing), treatment and precautions needed to prevent the spread of MDR Gram-negative bacteria. The guidance describes appropriate infection prevention and control precautions to include hand hygiene, equipment and environmental cleaning and guidance on screening for MDR Gram-negative bacteria. There is an accompanying guideline describing best practice in antimicrobial prescribing and stewardship which should be used in conjunction with this report.

The Working Party comprises a group of medical microbiologists and scientists, infectious disease physicians, infection control practitioners, epidemiologists and patient representatives. The patient representatives are lay members and have direct experience of the treatment of healthcare-associated infections through personal experience and/or through membership of the Healthcare-acquired Infection Service Users Research Forum, patient charities and/or through involvement in the development of National Institute for Health and Care Excellence (NICE) guidelines.

4. Guideline Development Team

4.1. Guideline Advisory Group

- Martin Kiernan, Nurse Consultant, Prevention and Control of Infection, Southport and Ormskirk NHS Trust, Southport, UK
- Phil Wiffen, Cochrane Pain, Palliative and Supportive Care Group Pain Research, Churchill Hospital Oxford, Nuffield Department of Clinical Neurosciences, Oxford, UK
- Karla Soares-Wieser, Enhance Reviews Ltd, Wantage, UK

4.2. Acknowledgements

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4.3. Source of funding

A grant from the British Infection Association (BIA), the Healthcare Infection Society (HIS) and the British Society for Antimicrobial Chemotherapy (BSAC) funded Karla Soares-Wieser and others at Enhance Reviews Ltd, Lyford, Wantage and Paul Wiffen to perform the systematic review.

4.4. Disclosure of potential conflict of interest

- APRW: Consultant on Drug Safety Monitoring Boards for Roche and Genentech. Advisory panel for 3M.
- DML: Advisory boards or consultancy for Achaogen, Adenium, Alere, Allecra, AstraZeneca, Basilea, Bayer, BioVersys, Cubist, Curetis, Cycle, Discuva, Forest, GSK, Longitude, Meiji, Pfizer, Roche, Shionogi, Tetraphase, VenatoRx and Wockhardt. Paid lectures for AOP Orphan, AstraZeneca, Bruker, Curetis, Merck, Pfizer and Leo. Relevant shareholdings in Dechra, GSK, Merck, Perkin Elmer and Pfizer (collectively amounting to $<$10% of portfolio value).
- JAO: Part-time employment at Bioquell during the production of these guidelines. Paid lectures for 3M. Research funding from Pfizer and the Guy's and St Thomas' Charity.
- PJ: Advisory board for Baxter.
- DAE: ECCMID conference attendance funded by Astellas and Eumedica.
- BO: Advisory board for Astellas and Forest. Lecture for Alere.
- CM: Travel expenses funded by Mérieux Diagnostics.
- MC: IPS conference attendance funded by corporate sponsorship from Mölnlycke Healthcare.
- PH: Consultancy for bioMérieux, Becton-Dickinson, Eumedica, Merck, Novartis, MagusCommunications, Pfizer and Wyeth. Director of ModusMedica (medical education company). Research funded by Merck, Novartis and Pfizer.
- All other authors declared no conflict of interest.

4.5. Relationship of authors with sponsors

BSAC, BIA and HIS commissioned the authors to undertake the Working Party Report. IPS provided additional panel members and financial support for them to attend meetings. The authors are members of these societies.

4.6. Responsibility for guidelines

The views expressed in this publication are those of the authors, and have been endorsed by the sponsoring societies following consultation.

5. Working Party Report

Date of publication: January 2016 (published online 16th November 2015)

5.1. What is the Working Party Report?

This report is a set of recommendations covering prevention of transmission of MDR Gram-negative bacteria (i.e. resistant to at least three different antibiotics).

Antimicrobial chemotherapy and stewardship are covered in a separate publication.

The Working Party recommendations have been developed systematically through a multi-professional group based on published evidence. They should be used in the development of local protocols for all acute and long-term healthcare settings.

5.2. Why do we need a Working Party Report for these infections?

Colonization and infection by MDR Gram-negative bacteria have become prevalent in some European countries. Heavy use of broad-spectrum agents selects for organisms with resistance, and increases their chance of spread. National antibiotic consumption is increasing in the UK (6% increase in 2013 compared with 2010).[4] The spread of these infections risks increasing the length of hospital stay, and has an adverse effect on the quality of care of patients. Public awareness of resistance and healthcare-associated infections is increasing, and the paucity of new antimicrobial agents to treat these infections has resulted in the formulation of the five-year Antimicrobial Resistance Strategy by the Department of Health for England to address the problem. When outbreaks of infection involving MDR strains occur, there is a considerable financial, physical and psychological cost. Unless controlled, outbreaks are likely to become more common and MDR strains will become endemic. Evidence-based infection prevention and associated quality improvement methods are effective in reducing the number of infections with these organisms.

5.3. What is the purpose of the Working Party Report's recommendations?

This report describes measures that are clinically effective for preventing infections when used by healthcare workers in acute and long-term health care.

5.4. What is the scope of the guidelines?

Two sets of guidelines have been developed. This report includes appropriate infection prevention and control precautions. The other report describes best-practice antimicrobial prescribing and stewardship.[5]

5.5. What is the evidence for these guidelines?

In the preparation of these recommendations, systematic reviews of peer-reviewed research were undertaken. Expert opinion was also derived from published guidelines subjected to validated appraisal.[3] Evidence was assessed for methodological quality and clinical applicability according to the protocols of the Scottish Intercollegiate Guidelines Network (SIGN).

5.6. Who developed these guidelines?

A group of medical microbiologists, scientists, infectious disease physicians, infection control practitioners, epidemiologists and patient representatives.

5.7. Who are these guidelines for?

Any healthcare practitioner can use these guidelines and adapt them for local use. Users are anticipated to include clinical staff (i.e. medical, nursing and paramedical staff) as well as healthcare infection prevention and control teams. The guidelines should be used to improve practice of infection prevention, and to help patients and their carers to understand the methods available to prevent acquisition of antibiotic-resistant bacteria.

5.8. How are the guidelines structured?

Each section comprises an introduction, a summary of the evidence base with levels, and a recommendation graded according to the available evidence.

5.9. How frequently are the guidelines reviewed and updated?

The guidelines will be reviewed at least every four years and updated if change(s) in the evidence are sufficient to require a change in practice.

5.10. Aim

The primary aim of this report was to assess the current evidence for prevention and control of MDR Gram-negative infections.

6. Summary of guidelines

The guidelines relate to MDR Gram-negative bacteria and have been derived from current best peer-reviewed publications and expert opinion. Table IV contains expert opinion. Each recommendation is associated with a class of supporting evidence, as follows.

6.1. Surveillance

1,2. The minimum susceptibility tests performed on all significant Gram-negative isolates should include meropenem; in addition, cefpodoxime should be tested for Enterobacteriaceae, and ceftazidime should be tested for *Pseudomonas* spp. Strong

3. Travel history (i.e. countries or known endemic areas visited within previous year) should be collected for all patients with carbapenemase-producing Gram-negative bacteria. Strong

4. Each healthcare organization should have access to robust microbiological arrangements for detecting and reporting all MDR Gram-negative organisms in routine clinical samples and for screening using highly-sensitive tests with a diagnostic turnaround time of $<$48 h. Conditional

6.2. Screening

5. Active screening rather than passive surveillance is recommended for high-risk specialties. Conditional
6. Patients at high risk of colonization or infection with carbapenem-resistant organisms include those admitted to intensive care units (ICUs) and from long-term care facilities (e.g. care homes). Conditional
7. Screening for rectal and wound carriage of carbapenemase-producing Enterobacteriaceae should be undertaken in patients at risk. Strong
8. All patients transferred from, or with a history of admission to, healthcare facilities with known endemic carbapenemase-producing Enterobacteriaceae in the preceding year should be screened. Strong
9. Screening for carbapenem-resistant *Acinetobacter baumannii* and MDR *Pseudomonas aeruginosa* is required in the management of outbreaks. Strong
10. A rectal swab (with visible material) or stool sample (and urine sample if catheter present) should be used for screening for MDR Enterobacteriaceae and *P. aeruginosa*. For *Acinetobacter* spp., skin sites should be sampled, or, if a catheter or endotracheal tube is present, urine or respiratory secretions should be sampled. Conditional
11. In the event of secondary cases of carbapenem-resistant Enterobacteriaceae, standard infection control precautions (SICPs) and contact precautions should be monitored and re-inforced among clinical staff. Screening of patients not identified as carriers should be repeated weekly and on discharge from affected units until no new cases are identified for more than seven days. Strong
12. Patients with previous samples with carbapenem-resistant or other MDR Gram-negative bacteria should be screened at the time of admission. Conditional

6.3. Prevention of transmission

13. In addition to SICPs, apply contact precautions for those patients who present an infection risk. Strong
14. Where possible, single-room isolation should be provided for patients with MDR Gram-negative bacterial infection/colonization, and contact precautions should be continued for the duration of their stay. Conditional
15. Use disposable gloves and gowns or aprons to care for patients with MDR Gram-negative bacteria: *A. baumannii*, carbapenem-resistant and extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, *P. aeruginosa*. Strong
16. Identify and place infected and colonized patients in single rooms where available in this order of priority: carbapenem-resistant Enterobacteriaceae, carbapenem-resistant *A. baumannii*, ESBL-producing *Klebsiella* spp., carbapenemase-producing *P. aeruginosa*, ESBL-producing *Escherichia coli* and other Enterobacteriaceae, AmpC Enterobacteriaceae. Strong
17. If insufficient rooms are available, cohort patients following local risk assessment. Conditional
18. 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. Strong

6.4. Cleaning and environment

19. Environmental screening should be considered where there is unexplained transmission of MDR Gram-negative organisms or a possible common source for an outbreak. Strong
20. Respiratory and other contaminated equipment should be decontaminated (or respiratory secretions discarded) away from the immediate bed area in designated cleaning sinks and not in handwash sinks. Strong
21. For *P. aeruginosa*, including MDR strains, at a minimum, in accordance with the organization's water safety plan, a risk assessment should be made when levels of patient colonization or infection rise in order to determine if point-of-use filters should be installed or if taps need to be changed. Strong
22. Terminal disinfection of vacated areas with hypochlorite should be used in the control of outbreaks of infection due to MDR Gram-negative bacteria. Conditional
23. Hydrogen peroxide vapour should be considered as an adjunctive measure following cleaning of vacated isolation rooms/areas. Conditional
24. The routine use of selective decontamination of the mouth or digestive tract is not recommended for control of MDR Gram-negative bacteria. Conditional

6.5. Miscellaneous

25. Monitor hand hygiene of all staff when patient cohorting is being applied. Strong

7. Implementation of these guidelines

7.1. How can the guidelines be used to improve clinical effectiveness?

The guidelines can be used to inform local infection prevention and control guidance, and to direct clinical decision-making. They provide a framework for clinical audit tools aiming to achieve quality improvement.

7.2. How much will implementation of the guidelines cost?

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 economics and quality of life. Screening and isolation will result in significant cost pressures where they are 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.

7.3. Summary of audit measures

The following are expressed as percentage compliance:

- All Gram-negative isolates requiring antibiotic treatment are to be tested for susceptibility to meropenem (or all blood isolates should be tested).
- The microbiology laboratory reports all patients infected or colonized with carbapenemase-producing Gram-negative bacteria to Public Health England (PHE) or an equivalent body.
- All patients colonized or infected with carbapenem-resistant Enterobacteriaceae and *A. baumannii* are placed under contact precautions within 6 h of identification.
- All patients colonized or infected with carbapenem-resistant Enterobacteriaceae and *A. baumannii* are placed under contact precautions in a single room or cohort for the duration of their stay.
- Travel history is obtained at the time of admission for all acute hospital patients, and patients from endemic areas are screened.

7.4. E-learning tools

Continuing Professional Development questions and model answers are listed for self-assessment in Appendix 4.

8. Methodology

8.1. Evidence appraisal

Methods were in accordance with SIGN 50[1] and the Cochrane Collaboration,[2] and critical appraisal was applied using AGREEII.[3] Accepted guidelines were used as part of the evidence base and to support expert consensus. Questions for review were derived from the Working Party Group, which included patient representatives in accordance with the PICO process.[1]

K. Soares-Wiesner of Enhance Reviews Ltd and Dr P. Wiffen of Pain Research and Nuffield Department of Clinical Neurosciences, Oxford University used a systematic review process. Guidelines and research studies were identified for each search question. Systematic reviews, randomized controlled trials and observational studies were included and assessed by two reviewers. In context, observational studies included non-randomized controlled studies, controlled before—after studies and interrupted time series.

All languages were searched. Search strategies for each area are given in the sections below. MeSH headings and free-text terms were used in the Cochrane Library (Issue 11 2012), Medline (1946—2012), Embase (1980—2012) and Cumulated Index of Nursing and Allied Health Literature (CINAHL) (1984—2012). On 23rd May 2014, an update search was conducted on Medline alone using the same strategy for references after 1st January 2013. Reference lists of included studies were searched. Two review authors independently screened all citations and abstracts identified, and screened full reports of potentially eligible studies (those that addressed review questions in primary or systematic secondary research or a clinical or in-use study). Disagreements were resolved by discussion, and rationales for exclusion of studies were documented. Pretested data extraction forms were used, and study characteristics and results were collected. Data were extracted from observational studies for multiple-effect estimates: number of patients, adjusted and unadjusted effect estimates with standard error or 95% confidence interval (CI), confounding variables and methods used to adjust the analysis. If available, data were extracted from contingency tables. Risk of bias was assessed using SIGN critical appraisal checklists. Interrupted time series were assessed using the Cochrane Effective Practice and Organisation of Care (EPOC) Group.[1,6] Quality was judged by reported details of protection against secular changes (intervention independent of other changes) and detection bias (blinded assessment of primary outcomes and completeness of data). For outbreak patterns associated with particular pathogens, the Working Party made additional searches of descriptive studies to extract effective interventions.

Clinical outcomes were mortality, effectiveness of treatment and length of hospital stay. Microbial outcome measures were decreases in the prevalence of multi-drug resistance among Gram-negative bacteria, or decreases in colonization or infection by specific Gram-negative pathogens. Risk ratios (RR) were used for dichotomous variables, and mean differences with 95% CI were used for continuous outcomes.[7] Analyses were performed using Revman 5.2.[8] SIGN summary tables were used.

Evidence tables and judgement reports were presented and discussed by the Working Party, and guidelines were prepared according to the nature and applicability of the evidence, patient preference and acceptability, and likely costs. The strength of evidence was defined by SIGN (Table I), and the strength of recommendation was adopted from GRADE (Grading of Recommendations Assessment, Development and Evaluation) (Table II). The grading relates to the strength of the supporting evidence and predictive power of the study designs, rather than the importance of the recommendation. Any disagreements between members were resolved by discussion. For some areas, only expert opinion is available; in such cases, a good practice recommendation has been made.

8.2. Consultation process

On completion, these guidelines were opened to consultation with the stakeholders listed in Appendix 1. The draft report was placed on the HIS website for one month. Views were invited on format, content, local applicability, patient acceptability and recommendations. The Working Party considered and collated comments, and agreed revisions.

9. Rationale for recommendations

9.1. Epidemiology

9.1.1. What is the definition of multi-drug-resistant Gram-negative bacteria?

For the purposes of this guideline, MDR Gram-negative bacteria were defined as having three or more antimicrobial

Table I
Levels of evidence for intervention studies[1,6]

1++	High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias.
1 +	Well-conducted meta-analyses, systematic reviews or RCTs with a low risk of bias.
1 −	Meta-analyses, systematic reviews or RCTs with a high risk of bias.[a]
2++	High-quality systematic reviews of case–control or cohort studies. High-quality case–control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal. Interrupted time series with a control group: (i) there is a clearly defined point in time when the intervention occurred; and (ii) at least three data points before and three data points after the intervention.
2+	Well-conducted case–control or cohort studies with a low risk of confounding or bias, and a moderate probability that the relationship is causal. Controlled before–after studies with two or more intervention and control sites.
2−	Case–control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal. Interrupted time series without a parallel control group: (i) there is a clearly defined point in time when the intervention occurred; and (ii) at least three data points before and three data points after the intervention. Controlled before–after studies with one intervention and one control site.
3	Non-analytic studies (e.g. uncontrolled before–after studies, case reports, case series).
4	Expert opinion. Legislation.

RCT, randomized controlled trial.
[a] Studies with an evidence level of '1−' and '2−' should not be used as a basis for making a recommendation.

Table II
Recommendation grading[1]

	Recommendation
Undesirable consequences clearly outweigh desirable consequences	Strong recommendation against
Undesirable consequences probably outweigh desirable consequences	Conditional recommendation against
Balance between desirable and undesirable consequences is closely balanced or uncertain	Recommendation for research and possibly conditional recommendation for use restricted to trials
Desirable consequences probably outweigh undesirable consequences	Conditional recommendation for
Desirable consequences clearly outweigh undesirable consequences	Strong recommendation for

resistance mechanisms affecting different antibiotic classes. For a full discussion of the definitions in use, please refer to the companion paper.[5]

9.1.2. Which Gram-negative bacteria cause infection control problems?

Opportunistic Gram-negative bacteria that present increasing resistance issues include Enterobacteriaceae (*E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., *Citrobacter* spp., Proteeae) and the non-fermenters, *P. aeruginosa* and *A. baumannii*. *Stenotrophomonas maltophilia* is inherently MDR in most cases, but a less common cause of cross-infection. Gonococci are Gram-negative bacteria and are increasingly resistant, but were excluded because relevant public health control actions are substantially different.

In this report, emphasis is placed on strains resistant to β-lactams, including carbapenems, cephalosporins and β-lactamase inhibitor combinations, and strains resistant to fluoroquinolones insofar as these are the core components of most therapies for severe infections. Aminoglycosides are most often used as adjuncts to β-lactam therapy in severe infection, whereas polymyxins are mainly used in cases where β-lactams cannot be used due to resistance. Resistance to these latter groups of agents should nevertheless prompt concern, especially where it is coupled with resistance to multiple β-lactams, as is often the case. Means of infection control remain the same irrespective of the specific resistance.

9.1.3. What are the relative contributions of community and hospital acquisition?

The mechanisms and time course of resistance accumulation by Gram-negative opportunists, both internationally and in the UK, are reviewed in a companion paper.[5] This introduction, rather, is concerned with the distribution of these resistance types in hospitals, long-term care facilities and the community. The distinction between these sectors is increasingly blurred, with many elderly patients moving back and forth between hospital and care homes,[9] and with hospital stays becoming shorter, so that healthcare-associated infections often become apparent after hospital discharge[10] or on re-admission. Consequently, MDR Gram-negative bacteria — including those producing carbapenemases — are

increasingly seen in general practice specimens, principally urine samples. Careful enquiry often reveals that the patient recently received secondary care. The period of time that may elapse from acquisition in hospital, often in colonization sites, to the development of an obvious infection in the community is variable, and different papers use different intervals when classifying infection diagnosed in the community as 'healthcare-associated'. Intervals of one to three months are commonly used to distinguish community acquisition from that acquired during hospital admission, but the literature shows that carriage, and the potential for infection, can persist for much longer periods (commonly one year); it is recommended that this longer period should be used.[11]

9.1.4. What is the evidence for reservoirs and spread of multi-drug-resistant Gram-negative bacteria in care homes and secondary care?

Enterobacteriaceae, *P. aeruginosa* and *Acinetobacter* spp., whether resistant or not, can all be transferred among vulnerable patients by staff vectors and contaminated equipment, leading to well-defined local clonal outbreaks.[12] Both *A. baumannii* and *Klebsiella pneumoniae* (by virtue of their capsules) can survive on dry surfaces, including hands.[13,14] MDR Enterobacteriaceae can colonize the gut, providing — without any symptoms — a reservoir for transfer to other body sites where infection may ensue, or transfer to other patients. The risk of transmission is increased if the carrier experiences diarrhoea or incontinence.

In general, and excluding particular high-risk clones discussed below, there is no evidence that MDR strains are more likely to be associated with cross-infection than other strains. Enterobacteriaceae that owe carbapenem resistance to combinations of ESBLs or AmpC β-lactamase activity together with porin loss are often thought to have impaired fitness, and to be less likely to spread among patients than those with carbapenemases, but cross-infection by porin-deficient Enterobacteriaceae has been reported from Italy, Korea and Portugal.[15—17] In a nested case—control study in the USA, mechanical ventilation, pulmonary disease, days of antibiotic treatment and colonization pressure were associated with acquisition of carbapenem-resistant Enterobacteriaceae.[18] Typing of *K. pneumoniae* in this study suggested clonal transmission within and between hospitals.

9.1.4.1. High-risk clones. Bacterial typing has revealed the role of 'high-risk clones' in the international spread of resistance.[19] For example:

- The majority of fluoroquinolone-resistant ESBL-producing *E. coli* causing infection in hospitals and the community belong to sequence type (ST) 131-B2-O25b.[20,21]
- The growing prevalence of *K. pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* in hospitals (e.g. in Israel, Italy and the USA) substantially reflects the clonal expansion of ST258 variants with KPC-2 or -3 enzymes.[22]
- In Russia, Belarus and Kazakhstan, there is extensive nosocomial spread of ST235 *P. aeruginosa*, with VIM-2 carbapenemase only susceptible to colistin.[23]

Except in the case of ST131 *E. coli* (where infection may be preceded by a long period of innocuous gut carriage), UK hospitals are minimally affected by these lineages, although both ST258 *K. pneumoniae* and ST235 *P. aeruginosa* have been recorded.[22,24] National clones that have achieved considerable traction in the UK include *A. baumannii* OXA-23 clone 1, recorded at >60 hospitals.[19,25] It remains uncertain whether this prevalence reflects site-to-site transfer via colonized patients, or the selection, at multiple sites, of a pre-existing but previously rare subtype of this very clonal species. Focusing infection control on specific types rather than resistances has not been explored for ESBL-producing *E. coli*.

E. coli ST131 has spread globally, and is transmitted within hospitals, families, through pets and long-term care facilities whilst being very rare in food animals. It is often resistant to fluoroquinolones and multiple other antimicrobials, as well as producing CTX-M ESBLs.[26] The lineage can be distinguished by serotyping and polymerase chain reaction (PCR).[27] Among faeces sent for culture from international travellers returning to the UK, many of which were from the Indian subcontinent, 18% contained ESBL *E. coli*, mainly with CTX-M-15 enzymes, and 2.1% had ST131 strains with ESBL.[28]

9.1.4.2. Plasmid outbreaks. In this situation, a plasmid or family of related plasmids disseminate(s) among strains of one or more species in a locale.[29,30] This is the case, for example, in the current spread of pKpQIL plasmids encoding KPC carbapenemases in and around Manchester.[31] Unlike in a clonal outbreak, the isolates are diverse in terms of species, strain and in their antibiograms, which also reflect the host strain and any other plasmid(s) carried. Single-strain clusters occur within this overall diversity, but do not come to dominate the picture as in a classical single-strain outbreak. It is inferred (although rarely proven) that frequent plasmid transfer among gut bacteria leads to the diversity of strains involved.[32] As there is no single 'outbreak' organism to target this scenario, it is more challenging for infection control teams than a classical outbreak. Moreover, it presents a greater recognition challenge to the microbiology laboratory; consequently, reliable and consistent application of SICPs is extremely important.

9.1.4.3. Outbreaks due to Pseudomonas aeruginosa contamination of water systems. Classical clonal outbreaks of hospital infection have a clear train of transmission if carriage is taken into account, and, assuming consistent application of contact precautions, can be controlled in a relatively short time if the strain(s) are not re-introduced.[12] However, a different epidemiology is seen occasionally, particularly with *P. aeruginosa* (MDR or not), when a single clone or small number of clones causes infections in multiple patients in a unit or hospital, often without obvious links, over a prolonged period, sometimes extending over several years and with gaps of months between cases.[33,34] Such instances often reflect contamination of the hospital plumbing system by the pseudomonas clone(s), and control may require modification/assessment, including, for example, replacing sinks and toilets with easier-to-clean models less prone to splashback, educating staff to reduce blockages and inappropriate storage, reviewing cleaning protocols, and reducing shower flow rates to minimize flooding.[35,36]

9.1.4.4. Long-term care facilities and the spread of multi-drug-resistant Enterobacteriaceae. Long-term care facilities are increasingly identified as reservoirs of antibiotic resistance, particularly for colonization. The data to support this

view are considerable but are not based on systematic surveillance, except in France, where the incidence of ESBL-producing Enterobacteriaceae infection per 1000 days in long-term care facilities increased from 0.07 in 1996 to 0.28 in 2005. This largely reflected the proliferation of *E. coli* with CTX-M enzymes, which were later recognized as representatives of the international ST131 clone.[37,38]

Long-term care facilities range from establishments offering assisted living to largely independent residents through to those providing complex medical support.[39,40] This spectrum of care varies between countries, reflecting healthcare organization and cultural factors.[41–43]

The distribution of incontinent and catheterized residents is likely to influence the transmission of Gram-negative bacteria, including those with multi-drug resistance. Variation may be very local; March *et al.* found that gut carriage of resistant bacteria varied across five subunits in one long-term care facility in Bolzano, Italy.[44] Overall, carriage was higher than in the hospital's geriatric unit, which perhaps had more knowledge and reliable application of infection prevention and control precautions (75% of 111 in long-term care facility vs 22% of 45 in geriatric unit). In contrast, Gruber *et al.* in Germany found higher carriage rates of MDR bacteria in geriatric units (32.6%) than in nursing homes (18.5%) or ambulatory care (15.6%).[45]

While most resistance studies on long-term care facilities relate to those caring for the elderly, spread of carbapenemase producers as gut colonizers has also been recorded in a care home for children and young adults with neurodevelopmental problems.[46]

The literature supporting the view that long-term care facilities constitute a reservoir of multi-drug resistance comprises, firstly, numerous analyses showing that previous stay in a long-term care facility is a risk factor for later infections with MDR Gram-negative bacteria, including those with ESBLs and carbapenemases; and, secondly, multiple snapshot surveys showing frequent (although very variable) gut carriage of ESBL-producing *E. coli* and *Klebsiella* spp. among residents in long-term care facilities, including in Australia, Belgium, France, Germany, Israel, Japan, Malaysia, the UK, Italy and the USA where these enzymes have already proliferated in hospitals.[44,47–51] Accumulation of MDR Gram-negative bacteria in long-term care facilities probably reflects a combination of:

- the frequent transfer into long-term care facilities of patients/residents who were initially colonized or infected in hospitals;
- oro-faecal transfer within long-term care facilities, reflecting breakdowns of personal hygiene in populations with high rates of dementia and incontinence;
- frequent antibiotic use and its contingent selection pressure on the gut flora; and
- high rates of urinary tract catheterization.

Only one sizeable UK study of the carriage of MDR Gram-negative bacteria by nursing home residents has been published.[9] This was conducted in Belfast from 2004 to 2006, early in the national dissemination of *E. coli* with CTX-M ESBLs. This study included 16 long-term care facilities, and found *E. coli* that were both ciprofloxacin-resistant and produced ESBLs in faeces from 119 of 294 residents (40.5%). This was a 40-fold higher carriage rate than for diarrhoeal samples from community patients. Virtually all (99%) of these MDR isolates were ST131 variants; half belonged to the CTX-M-15-positive 'strain A' variant that is common elsewhere in the UK.[52,53] Two small (six- and 12-bed) long-term care facilities had no colonized residents, and others had up to 75% (18/24) colonized residents, with considerable diversity among the ST131 variants at many sites. Fluoroquinolone use and a history of urinary tract infection were independently associated with carriage in a multi-variate model.[9] Duration of nursing home residency did not correlate with increased likelihood of carriage, although it seems likely that carriers commonly acquire their organism within their long-term care facilities.

9.1.5. Multi-drug resistance in the community

Multi-drug resistance remains uncommon among true community-acquired infections in the UK, and few studies have correlated resistance in clinical infections and faecal carriage in these cases. Nevertheless, stool carriage of ESBL-producing faecal *E. coli* was found in 11.3% of patients in Birmingham, rising to 22.8% in those with surnames suggesting a Middle Eastern or South Asian patrimony compared with 8.1% among names suggesting European patrimony. This differential perhaps reflects frequent travel to parts of the world where ESBLs are common outside the hospital setting.[54] A few references specifically indicated travel to South or East Asia as a risk factor for acquisition of ESBL-producing *E. coli* in faeces. Carriage is often persistent and, in Canada, prior travel to a country with a high prevalence of ESBL-producing *E. coli* was identified as a risk factor for subsequent urinary infection with these organisms, typically with the particular ESBL type prevalent in the country visited.[55]

Most cases of infection or colonization by carbapenemase-producing Enterobacteriaceae and non-fermenters occur in hospital and healthcare settings, at least in Europe and North America.[22,56–58] However, in areas of high prevalence, particularly parts of the Indian subcontinent, it seems that a large reservoir of community carriers of carbapenemase-producing Enterobacteriaceae has been established, which likely eclipses the hospital-based reservoir in terms of numbers, but not risk.[59,60]

MDR *P. aeruginosa* and other non-fermenters are an important problem in patients with cystic fibrosis, who also span the hospital/community divide. There is a growing prevalence of high-risk clones, such as the Liverpool epidemic *P. aeruginosa* strain.[61] Cross-infection occurs[62] and can be interrupted by segregation of colonized and non-colonized patients with cystic fibrosis.[63] Resistance is often extensive but evolves very variably in the individual patient, and there is no specific resistance pattern associated with any of the successful cystic fibrosis lineages.[64]

9.1.6. What is the role of agricultural use of sewage and antibiotic treatment in veterinary practice in spreading extended-spectrum β-lactamases?

Gut *E. coli* are ubiquitous in mammals, and MDR strains are reported repeatedly in both food and companion animals.[65] Johnson *et al.* demonstrated that the same ESBL-producing *E. coli* strains can be shared among household members and their pet dog, although the direction of transmission is uncertain.[66] Transmission of resistant *E. coli* down the food chain can occur. At a population level, fluoroquinolone-resistant *E. coli* from chickens and humans were reportedly more similar than fluoroquinolone-resistant and -susceptible *E. coli* from

humans.[67] However, sequence typing needs to be examined. In the Netherlands, the same *E. coli* strains, plasmids and ESBL genes ($bla_{CTX-M-1}$ and bla_{TEM-52}) were found in humans, broilers and retail chicken meat.[68] However, the ESBLs in retail chicken meat in the UK are predominantly CTX-2 or -14-like,[69,70] and their host strains are non-clonal, whereas clonal ST131 *E. coli* with CTX-M-15 enzyme predominates among human ESBL isolates and is very rare in chicken meat.

Recently, a large UK, German and Dutch study found that only 1.2% of ESBL-producing *E. coli* from food animals resembled human ESBL-producing isolates. The authors concluded that human-to-human faecal-oral or plasmid transmission was considerably more important than food chain transmission, but noted that food animals represent a reservoir (and evolution site) for resistant strains that may pose future challenges in humans.[71]

9.1.7. What insights have national Escherichia coli bacteraemia surveillance provided?

Bacteraemias caused by *E. coli* result from a variety of aetiologies including pre-existing urinary tract infection, indwelling urinary catheters and biliary-related infection. In sentinel surveillance undertaken by PHE, most cases arose in elderly patients in the community who had visited their general practitioner at least once in the preceding weeks with urinary tract infection, suggesting that co-morbidity or treatment failure may be a significant factor.[72] One-third of patients with bacteraemia had received antibiotics for genitourinary infection in the preceding four weeks, but the adequacy of treatment was not known. There is a notable rise in incidence in the summer for all Gram-negative bacteraemias,[73–76] and a number of hypotheses are possible, including the role that hydration status in the elderly has to play in predisposition to infection. Reporting resistance data in *E. coli* bacteraemia helps in making local risk assessments on patients transferred from other hospitals.[77]

9.1.8. Is there evidence for high-/low-risk areas within a healthcare facility?

Sharing a room with a colonized patient and ICU admission are risk factors for acquisition of carbapenem-resistant organisms.[78–80] A German point prevalence study of 56 hospitals in 2011 showed that, overall, prevalence of resistance was highest in ICUs (ESBL-producing *E. coli* 2.5% on ICU) and higher on medical wards compared with surgical wards,[81] as also seen in a UK study.[82] A European survey of 19,888 patients, mainly in Belgium and France, showed the highest prevalence of healthcare-acquired infection in ICUs (28.1%).[83]

Long-term care facilities report high prevalence of colonization with MDR Gram-negative bacteria in residents compared with acute hospitals, associated with prolonged stay, antimicrobial treatment and faecal incontinence.[84,85] In one series of carbapenem-resistant *Acinetobacter* and *Klebsiella* isolates, over half were obtained from patients admitted from long-term acute care facilities.[86]

Evidence

ICUs in acute hospitals and any long-term care facilities have higher prevalence of MDR Gram-negative bacteria than general wards. 2+

Recommendation

Patients at high risk for colonization or infection with carbapenem-resistant organisms include those admitted to ICUs and from long-term care facilities (e.g. care homes). Conditional

9.2. Is there evidence of differences between organisms in respect of transmission, morbidity and mortality?

9.2.1. Resistant Enterobacteriaceae

Enterobacteriaceae are part of the gastrointestinal flora of humans and animals, and some are readily transmitted, particularly in the healthcare setting (Table III). It remains unclear why the *E. coli* ST131 lineage has been so successful compared with many other ESBL-producing strains.[87] Transmission from patient to patient is believed to be mainly via hands of staff, although common environmental sources have occasionally been described and should be sought where no other plausible vectors can be found (e.g. ventilator equipment or water supply).[12,35,88,89] Infection prevention and control relies on the consistent application of SICPs (e.g. hand hygiene, appropriate use of personal protective equipment, and ensuring a clean and well-maintained care environment). Patient screening, used as part of a bundle of infection prevention and control measures, is effective for identifying carriage of ESBLs by *E. coli*, *K. pneumoniae* and *Enterobacter* spp.[90–92]

For colonization or infection with ESBL-producing bacteria, the presence of a gastrostomy, urinary catheter or nasogastric tube were risk factors.[93–95] Antibiotic treatment has been shown to select for ESBL-producing *E. coli* in a variety of healthcare settings.[96] For some strains, piperacillin-tazobactam can select for quinolone-resistant bacteria that produce CTX-M,[97] and carbapenem use is associated with acquisition of carbapenem-resistant *E. coli*.[98]

Screening for carriers with subsequent isolation of those identified is effective in preventing transmission, and is important for early recognition.[99] Awareness of carriage is important and, therefore, communications regarding those identified to be infected or colonized with MDR strains is essential when transferring patients within and between institutions.

9.2.2. Acinetobacter baumannii

Infection control precautions against *A. baumannii* have been adapted following experience with outbreaks, and generally address the organism's major epidemic modes of transmission and the excessive use of broad-spectrum antibiotics (Table III). Control can sometimes be achieved when a common source is identified and eliminated.[12,100] A review of 51 hospital outbreaks showed that 25 had common sources. Of these, 13 outbreaks were predominantly respiratory tract infections, and 12 were predominantly bloodstream or other infections. They were controlled by removal or disinfection and sterilization of contaminated ventilator (or related) equipment or contaminated moist fomites.[12]

When neither common sources nor environmental reservoirs are identified, control has depended on surveillance and isolation of colonized and infected patients, along with promoting improvements in the hand hygiene practices of healthcare workers,[101] and ensuring the aseptic care of vascular catheters and endotracheal tubes.[12] Increased cleaning of the general care environment has been the next most common outbreak

intervention,[12] reflecting the concern that *Acinetobacter* spp. can survive for months on wet or dry surfaces, thereby facilitating nosocomial transmission.[102] Disinfection regimens used on surfaces include 0.1% hypochlorite[103,104] and, increasingly, hydrogen peroxide vapour.[105–109]

Patient screening has been suggested in a number of studies.[104,110,111] Several studies also advocate reduced prescribing of broad-spectrum antibiotics, such as fluoroquinolones or carbapenems.[12,112] Antibiotic exposure is often a risk factor for an outbreak; however, the use of multiple interventions and historical controls complicates interpretation of these studies. Patient decolonization by skin cleansing with chlorhexidine or the use of polymyxin on wounds, orally or by inhaled aerosol, has been an occasional adjunctive control measure but may be a risk for development of resistance.[113–115] Often, the use of a multi-factorial or 'bundle' approach is the most effective way of controlling this organism.[116]

9.2.3. *Pseudomonas aeruginosa*

Sources and mechanisms of transmission vary, and surveillance is complicated by the close association between patient and environmental isolates. Association with moist environmental sources is well documented, although significant persistence on dry surfaces, including hospital linen and floors, with a range of 6 h to 16 months is reported.[117] Water systems act as a source of infection, or indicate environmental contamination from other sources (e.g. staff hands or re-usable care equipment being cleaned in handwash sinks).[34] Levels of sink colonization are higher in critical care areas than general wards.[118]

Transmission occurs via the hands of healthcare workers, contaminated either from patients or from the environment, and has been reviewed systematically by Loveday.[34,119–124] Pseudomonal carriage on hands may be less persistent than for other Gram-negative bacteria, but other factors such as glove usage and artificial nails contribute.[13,125–127] Patient-to-patient transmission can occur via the air among patients with cystic fibrosis, with evidence of infectious droplet nuclei,[128] or via patient hand and environmental contamination.[129,130]

Sporadic and epidemic strains tend to co-exist and may be difficult to track without molecular typing.[124,131] There is no evidence for the effect of routine surveillance on the control of MDR *Pseudomonas* spp., but reports of outbreak interventions support the utility of screening.[132,133]

There is little evidence that isolating patients in single rooms reduces endemic MDR *Pseudomonas* spp. levels. In outbreak settings, use of isolation measures as part of a multi-faceted infection control regime is usual, but direct evidence for the impact of isolation alone is lacking.[132,134–138] There is a risk of bias in outbreak reports, and balance between desirable and undesirable effects of physical isolation should be considered. There is a poor level of specific evidence as to the effect of hand hygiene, but expert opinion extrapolated from other situations supports the use of this measure as part of a wider infection prevention strategy.[33,132,133,138,139] Care should be exercised with production, storage and turnover of cleaning products as the organism has a degree of tolerance to disinfectants, and there is evidence for pseudomonal contamination of detergent-type cleaning products.[140,141]

9.3. Surveillance

9.3.1. Selection of samples and antimicrobials to test

In order to support surveillance and infection control, national uniformity is needed in the testing of clinically significant isolates and in the detection of MDR strains. This may involve widespread testing of organisms with antibiotics that would not ordinarily be used in the individual patient.

In particular, testing of parenteral agents against urinary Gram-negative isolates from community patients is necessary. This may impose costs on diagnostic laboratories without matching benefits beyond earlier detection of spread of such infections. At present, the major requirement is detection of carbapenem-resistant organisms, although detection of quinolone-resistant and ESBL-producing organisms is important. Plasmid transmission of carbapenemases to a wide variety of Gram-negative species makes it difficult to be proscriptive. Validated, sensitive algorithms for testing need to be developed if universal testing is not applied. Testing cephalosporin-resistant isolates solely for carbapenem resistance may miss strains with OXA-48 carbepenemases, but this is a useful minimum standard for detection of other carbapenemases. Wider testing of temocillin may detect more OXA-48-producing strains.[142]

The basic phenotypic strategy to detect carbapenemase producers is to use a carbapenem as an indicator, and then to undertake supplementary tests to distinguish carbapenemase producers from those that have other carbapenem resistance mechanisms.[143] Some carbapenemases may not be associated with clinical resistance to carbapenems, and tests that detect hydrolytic capacity [e.g. the modified Hodge/clover leaf test, or synergy tests between carbapenems and boronates (to inhibit KPC enzymes) or EDTA (to inhibit metallo-carbapenemases)] are more useful in identifying these strains. European Committee on Antimicrobial Susceptibility Testing (EUCAST) advice is that Enterobacteriaceae with a minimum inhibitory concentration (MIC) for meropenem >0.12 mg/L should be treated with suspicion, not just those with MICs above the clinical breakpoint of 2 mg/L; the screening MIC of >0.12 mg/L equates to a zone with a diameter of <25 mm on Mueller-Hinton agar.[144] Ertapenem is a more sensitive indicator of carbapenemase production than meropenem or imipenem, but is less specific as it is affected more than other carbapenems by porin-mediated mechanisms. It is also less used and tested. Meropenem or imipenem have better specificity and are to be recommended for screening for national surveillance. EUCAST screening breakpoints should be used.[143]

Many laboratories do not test meropenem susceptibility routinely for all Gram-negative blood isolates. For national surveillance of carbapenem resistance to be effective, phenotypic meropenem resistance must be tested for all blood isolates, and resistance must be reported to central authorities. However, provision for reporting meropenem-resistant Gram-negative isolates from all body sites is important, and should not burden laboratories excessively; electronic and paper reporting systems should be made available. All secondary and tertiary care hospitals, as well as private hospitals, should be included. Monitoring by identifying specific carbapenemases would require reference laboratory reports; therefore, local confirmatory tests are encouraged. Automated PCR methods are being developed or available for specific carbapenemase gene detection, but are not yet widely used. Most meropenem resistance in *P. aeruginosa* is due to loss of

Table III
Dissecting the epidemiology of multi-drug-resistant (MDR) Gram-negative rods

	Resistant Enterobacteriaceae		MDR non-fermenters		
	AmpC, ESBL	CPE	*Acinetobacter baumannii*[a]	*Pseudomonas aeruginosa*	*Stenotrophomonas maltophilia*
Microbiology	Fermentative, oxidase-negative, motile or non-motile, facultatively anaerobic, rods		Non-fermentative, oxidase-negative, non-motile, obligate aerobic, coccobacilli[330]	Non-fermentative, oxidase-positive, motile, aerobic, rods[331]	Non-fermentative,[b,332] motile, oxidase +/−, obligate aerobic, rods[333]
Reservoirs	Human and animal gastrointestinal tract, water		Respiratory and gastrointestinal tract, dry surfaces[330,334]	Ubiquitous: plants, animals, moist environments[331]	Ubiquitous: plants, animals, humans, moist environments[333,335]
Sites of colonization	Gastrointestinal tract[22]		Skin, respiratory and gastrointestinal tract[187,334,336]	Gastrointestinal tract, moist body sites (throat, nasal mucosa, axillary skin, perineum)[337]	Respiratory and gastrointestinal tract[333,335,338]
Duration of colonization	Months to more than one year[339–341]		Days to weeks[334]	—	—
Clinical manifestation	Urinary tract (e.g. *E. coli*), pneumonia (e.g. *K. pneumoniae* and *Enterobacter* spp.), intra-abdominal infection[337,342]		Ventilator-associated pneumonia, catheter-related bloodstream and urinary tract infections, wound infections[330,334]	Pneumonia, urinary tract, surgical site, bloodstream infections, cystic fibrosis lung, burns[331]	Pneumonia, bloodstream infections; less commonly, urinary tract and wound infections[333,335]
Environmental survival	Hours to weeks on dry surfaces;[117] contaminated environment likely to play a minor role in transmission[252,263]		Weeks to months on dry surfaces;[117,251] difficult to remove from surfaces by cleaning and disinfection[103,106]	Contaminates moist hospital environments: tap aerators, respiratory therapy equipment[337]	Contaminates moist hospital environments; can form biofilms on surfaces; low biocide susceptibility[333,335]
Transmission routes	Hands (++), contaminated surfaces (+/−)[319]		Contaminated surfaces (++), hands (+), air (+/−)[31,252,334]	Hands (+), contaminated moist surfaces (+), air (+/−), water systems[337,343]	Hands (+), contaminated moist surfaces (+), air (+/−)[333,343]
Antimicrobial resistance — intrinsic	Ampicillin, first- and second-generation cephalosporins.[344] *Serratia* and *Proteeae* spp. are intrinsically resistant to polymyxins		Ampicillin, amoxicillin-clavulanate, cefazolin, cefotaxime, ceftriaxone, ertapenem, trimethoprim, fosfomycin[330]	Some β-lactams and fluoroquinolones, macrolides, tetracyclines, cotrimoxazole[345]	Most agents except cotrimoxazole[333,335]
Antimicrobial resistance — acquired	Penicillins (except temocillin), ESBLs, carbapenems (through mechanisms other than more common acquired carbapenemases), aminoglycosides, sulphonamides, quinolones[344,346]	Most or all β-lactams, carbapenems, polymyxins (rarely) (exact profile depends on particular carbapenemase and any co-produced ESBL)[31,347]	Quinolones, aminoglycosides, β-lactams (including carbapenems), polymyxins, tigecycline[330,348]	Aminoglycosides, β-lactams (including carbapenems), monobactams, fluoroquinolones, polymyxins[345]	Trimethoprim/sulfamethoxazole

Common acquired resistance enzymes	AmpC (intrinsic in Enterobacter), ESBLs (TEM, SHV, CTX-M), various aminoglycoside-modifying enzymes	Carbapenemases (KPC, VIM, IMP, NDM)[22]	Various aminoglycoside-modifying enzymes or ribosomal methyltransferase, class-D OXA type carbapenemases[330,349]	Metallo-β-lactamases (VIM and IMP)[345]	*sul* genes (resistance to sulphonamide)
Mortality (bacteraemia)	Moderate/substantial increase in attributable mortality[342,350]	Stark increase in attributable mortality[22,262,351]	Minimal increase in attributable mortality[350]	Moderate/substantial increase in attributable mortality depending on type of infection[350,352]	Minimal increase in attributable mortality[353]
Risk factors	Hospital: prolonged hospital stay, prior hospitalization, previous use of antibiotics, presence of indwelling catheters, mechanical ventilation Community: older age, recurrent urinary tract infections/prior invasive procedures (e.g. catheterization), known faecal carriage, contact with healthcare facilities, antimicrobial treatment[143]	Prior antimicrobial use, length of stay, severity of illness, mechanical ventilation, admission to ICU, high procedure score, presence of wounds, positive culture from a blood isolate, transfer between hospital units within the same hospital, prior surgery, prior hospital stay, proximity to other colonized/infected patients, presence of a biliary catheter and recent transplantation.[168] For NDM, prior hospitalization on Indian subcontinent; for OXA-48, prior hospitalization in Middle East	(i) Major trauma, particularly burns, surgery and battlefield injury; (ii) previous antimicrobial therapy; (iii) prolonged hospital and ICU stay; (iv) mechanical ventilation, drainage tubes and indwelling catheters; (v) high prevalence of MDR *Acinetobacter* spp. on the unit; (vi) proximity to other colonized/infected patients[330,349]	(i) Prior use of antibiotics; (ii) mechanical ventilation; (iii) prolonged hospital and ICU stay; (iv) co-morbidities (e.g. cystic fibrosis, burns units)[352,354]	Severely compromised health status, malignancy, indwelling devices (such as intravascular catheters and ventilation tubes), exposure to broad-spectrum antimicrobials, long hospital stay, ICU stay[333,335]
At-risk population	Patients in acute, long-term and community settings; patients travelling to areas of high prevalence[56]	Patients in acute settings, particularly those with recent travel to areas of high prevalence[22,355]	Immunocompromised patients in the ICU and burns units;[330] rare cause of community-acquired infection[334,356]	Immunocompromised patients in the ICU and burns units; patients with cystic fibrosis;[345] rare cause of community-acquired infection[337]	Immunocompromised patients in the ICU; patients with cancer and cystic fibrosis; rare cause of community-acquired infection[333,357]
Common international clones	*E. coli* ST131 with CTX-M ESBLs[19]	*K. pneumoniae* ST258 with KPC enzymes[19,22]	International clones I–III[19,330]	Clonal diversity.[19] A few international high-risk clones [e.g. ST111 (serotype O12)] acquire multi-drug resistance; spread of ST235 with VIM carbapenemase in Russia, Belarus and Kazakhstan	Clonal diversity[333,335]

KPC, *Klebsiella pneumoniae* carbapenemase; *E. coli*, *Escherichia coli*; *K. pneumoniae*, *Klebsiella pneumoniae*; ESBL, extended-spectrum β-lactamase; CPE, carbapenem-producing Enterobacteriaceae; ICU, intensive care unit.

[a] From a taxonomic viewpoint, four species are virtually indistinguishable (*A. baumannii*, *Acinetobacter calcoaceticus*, genomic species 3 and genomic species 13TU) so are grouped together as '*A. calcoaceticus–A. baumannii* complex'; however, *A. baumannii* is by far the most important human pathogen in this group. However, as methods commonly used to speciate *Acinetobacter* spp. in the clinical laboratory are unable to distinguish these species, the relative contribution of each to the burden of human disease is difficult to establish.

[b] Recent data indicate that the 'non-fermentative' status of *S. maltophilia* should be re-assessed.

OprD porin and not a carbapenemase. Sensitivity to ceftazidime, piperacillin-tazobactam and carbenicillin despite meropenem resistance suggests this mechanism, and also suggests that neither high-level infection control action nor submission to a reference laboratory is needed.

To detect ESBLs, *E. coli*, *Klebsiella* spp. and *Proteus mirabilis* should be screened for clavulanate-reversed resistance to ceftazidime and cefotaxime[143] or cefpodoxime. AmpC producers are resistant to cefotaxime (reversed by cloxacillin), but susceptible (or intermediate) to cefepime. For AmpC-inducible genera, such as *Enterobacter* spp. and *Citrobacter freundii*, comparison of cefepime and cefepime plus clavulanate discs can be used to detect additional presence of ESBLs. Confirmation of ESBL production is most easily accomplished by comparing inhibition zones for discs with cephalosporin alone with discs containing clavulanic acid. A zone expansion of >5 mm indicates ESBL production. Alternatively, an Etest strip is used to demonstrate at least eight-fold reduction in MIC.

Faster diagnostic methods may be considered, particularly during outbreaks, to allow more rapid isolation. Selective media or combinations of non-selective media and a chromogenic or genetic test achieve a result within 24 h. Detection within a few hours is possible if molecular tests are applied directly to the clinical specimen, although this approach is still new.

Various selective commercial media are available to seek ESBL, CTX-M ESBL or carbapenemase producers directly from clinical specimens or early growth in blood culture bottles. Media-seeking ESBL producers often have good sensitivity but poor specificity in distinguishing these organisms from strains that hyperproduce AmpC enzymes.[145–147] The sensitivity of media-seeking carbapenemases varies with the particular enzyme,[148] with OXA-48 being the most difficult to detect due to the low levels of resistance often conferred. The alternative approach is to seek ESBL or carbapenemase activity in colonies growing on non-selective agars. Colorimetric and biochemical approaches include the following:

- The chromogenic oxyimino-cephalosporin HMRZ-86 turns from yellow to red on hydrolysis.[149] If used in combination with inhibitors, it can be used to distinguish strains with AmpC, ESBLs or metallo-carbapenemases, although KPC enzymes may be confused with AmpC and it is unclear whether OXA-48 is detected.
- Acidimetric β-lactamase tests can be adapted to detect carbapenemase producers, as in the 'Carba-NP' test where, again, some authors report problems in detecting OXA-48.[150–152]
- MALDI-ToF assays for carbapenemase activity, exploiting the molecular mass change that occurs when the β-lactam molecules are hydrolysed.[153]

Molecular tests can be used to seek β-lactamase genes in overnight cultures. One PCR/array system (Check-MDR CT03) can rapidly detect a wide range of relevant acquired AmpC, ESBL and carbapenemase genes, distinguishing between those encoding classical and extended-spectrum TEM and SHV types.[154]

PCR may be used directly on rectal swabs, without culture, and can give results within 1h of the specimen being taken.[155] Sensitivity and specificity are good, although positive results are often obtained for patients from whom the laboratory fails to grow a carbapenemase-producing pathogen.[156] This is a wider issue with molecular diagnostics when used directly on specimens, and may either indicate a poor positive predictive value or that the culture is not the 'gold standard'.[157]

Recommendation

The minimum susceptibility tests performed on all significant Gram-negative isolates should include meropenem; in addition, cefpodoxime should be tested for Enterobacteriaceae, and ceftazidime should be tested for *Pseudomonas* spp. Strong

9.3.1.1. When to seek reference laboratory typing of isolates

- To inform cross-infection and outbreak investigations.
- To seek a particular type associated with specific clinical characteristic(s) (e.g. K1 capsular type of CC 23 of *K. pneumoniae* associated with hypermucoviscosity and liver abscesses).
- To provide national/international context (e.g. in tracking the spread of 'high-risk clones', such as ST258 *K. pneumonia*, with KPC carbapenemases).

Typing results can never stand alone, and need to be interpreted in the context of all available epidemiological, clinical and demographical data.[158] Typing of isolates is helpful to inform cross-infection and outbreak investigations among groups of patients with potential links. Comparison of isolates without epidemiological linkage information may result in patients being linked in error, simply because they share the same international high-risk clone, or both have representatives of a widespread cluster. Typing of environmental isolates may be helpful, especially where a piece of equipment common to all the affected patients is implicated. However, it may also be confusing and needs to be focused. All environmental samples should have a clear link to an affected patient; there is no point in typing environmental isolates on their own. Isolates from sink plug holes/drains may well match patient isolates, but this provides little information regarding the source as the isolate is likely to have come from the patient rather than the patient having acquired it from a drain. Large-scale environmental sampling is rarely helpful, and there should be a clear hypothesis as to a likely source and the link between that source and the patient(s).

9.3.2. What national surveillance is performed and how should it be developed?

National surveillance of antimicrobial resistance is essential in detecting the emergence of new strains and resistance mechanisms, providing information for formularies and assessing the effect of control strategies. Outputs must be timely and tailored to the needs of medical and nursing staff, healthcare organizations and commissioners of health care. The World Health Organization (WHO) provides WHONET database software, which is used for collecting data in some areas, while the European Antimicrobial Resistance Surveillance Network (EARS-NET) provides resistance information on blood and cerebrospinal fluid isolates across Europe.[159] EARS-NET identified the early accumulation of carbapenemases in *K. pneumoniae* in Greece,[160] although they are now also

proliferating in other countries such as Italy. As such, travel history on admission can be a useful indicator of risk of carriage of MDR organisms.

In the UK (except Scotland), PHE collects susceptibility data in a voluntary scheme for bloodstream isolates of all species. The Second Generation Surveillance System is a web-enabled database application that collects both communicable disease reports (which were previously collected by the UK CoSurv system and include bloodstream isolates) and antimicrobial resistance reports (which were previously collected by the UK AmSurv system).[159] Antimicrobial resistance reporting is voluntary and only applies to England, but now covers over 80% of laboratories. In May 2015, an enhanced surveillance system for the surveillance of carbapenemase-producing Gram-negative bacteria was launched. In addition, the BSAC Resistance Surveillance Project (http://www.bsacsurv.org) tracks the prevalence of antibiotic resistance for a range of species and antibiotics in bacteraemia and lower respiratory tract infection, based on collection and central testing of isolates from a panel of 40 laboratories across the UK and Ireland.

Evidence

There is a significant increasing trend of carbapenem-resistant *K. pneumoniae* and other Gram-negative bacteria in most European countries, with major proliferation in Greece and Italy, suggesting a risk of occurrence in the UK. 2+

Recommendations

Laboratories should test meropenem susceptibility in all clinically significant Gram-negative isolates. Strong

Travel history (i.e. countries or known endemic areas visited within previous year) should be collected for all patients with carbapenemase-producing Gram-negative bacteria. Strong

9.3.3. How should we undertake local screening, why is it important and how should it be interpreted?

Screening at hospital level is useful for infection control, and to track resistance types (e.g. carbapenemase producers) by rectal swab or stool on admission, weekly during hospital stay and at discharge (Table III). Rectal swabs have maximum sensitivity for MDR pathogens (other than *Acinetobacter* spp.), but it is critical to ensure the compliance of staff with guidance on how and when to take samples by means of audit and feedback, as well as the specific actions arising from a positive result.[161] When a carbapenem-resistant organism is identified (or an isolate with any other index resistance is sought), any epidemiologically-linked patients should be screened. Screening of other patients depends on an assessment of risk of shedding of the organism and duration of exposure, and is less likely to be required if the patient has been isolated from admission.[162]

The primary purpose of local screening is the detection of outbreaks of resistant colonizing or infecting organisms with minimum delay. Few hospitals have sufficient single rooms to allow segregation of all patients at risk when they are admitted. Therefore, local identification of carriers allows prioritization of single rooms, potentially limiting spread. Hospital-level surveillance provides faster notification of an emergent problem than awaiting results from the reference laboratory, particularly if a single clone and species is responsible. Passive surveillance of clinical infections alone will be too delayed to help to limit spread. In an outbreak, isolation and infection control precautions are only effective if combined with active surveillance.[161] A plasmid-based outbreak (e.g. carbapenemase producers) can be more difficult to recognize because multiple bacterial species may be involved.

9.3.4. At what point should passive surveillance switch to active surveillance (screening)?

Examination of routine diagnostic tests or discharge summaries requires few resources compared with screening an entire 'at-risk' group. However, screening quickly identifies patients colonized with MDR Gram-negative pathogens who require source isolation but who might otherwise be placed in a shared bay. Choosing to screen depends on available resources, outbreak progression and clinical characteristics. Current national advice to screen patients at risk for carbapenemase-producing Enterobacteriaceae is made despite a low prevalence of these organisms in most UK centres because the clinical risk of spread is thought to be high.[162]

Passive surveillance of routine cultures did not distinguish 12 (86%) of 14 patients later found to have faecal carriage of carbapenemase-producing *K. pneumoniae*.[163] MIC was highly dependent on the inoculum. On average, routine cultures identify patient carriage of ESBL Enterobacteriaceae three days later than active screening.[164] The virulence of the strain, host susceptibility and the sensitivity of the diagnostic method will affect the efficiency of passive identification of patients.[161] As such, no single recommendation can be made.

Evidence

Passive surveillance is less sensitive and slower in identifying outbreaks of MDR Gram-negative infections than active screening. 3

Recommendation

Active screening rather than passive surveillance is recommended for high-risk specialties. Conditional

9.4. What is the evidence that infection prevention and control precautions prevent transmission?

Trials of infection control strategies are difficult to mount with sufficient power to determine efficacy, and most trials use a package of measures so the effect of single interventions cannot be extracted. A systematic review of infection control precautions in care settings for patients receiving stem cells or treatment for cancer showed a combination of prophylactic antibiotics, control of air quality and isolation in a room was associated with a lower rate of mortality [odds ratio (OR) 0.60, 95% CI 0.50–0.72] at 30 days.[165] Gram-negative bacteraemia was reduced by the package of measures. Gram-negative infections were significantly less common in patients who were isolated, but there were insufficient data to assess the specific effect on MDR strains. Environmental cleaning and screening are discussed in other sections.

9.4.1. Are standard infection control precautions sufficient to stop transmission?

Existing national guidelines are unequivocal that SICPs should be used by all staff, in all care settings, at all times, for all patients (adults, children and infants), whether infection is known to be present or not, in order to ensure the safety of

those being cared for, staff and visitors in any environment where care is given. SICPs are the basic infection prevention and control measures necessary to reduce the risk of transmission of infectious agents from both recognized and unrecognized sources of infection.

Sources of (potential) infection include blood and other body fluid secretions or excretions (excluding sweat), non-intact skin, mucous membranes, and any equipment or items in the care environment that could have become contaminated.

To be effective in protecting against infection risks, SICPs must be used continuously by all staff. Patients who move frequently between the hospital, the community and long-term care facilities may render location-based screening inadequate as a means to identify outbreaks.

However, as underscored by recent systematic reviews,[166,167] there is a paucity of evidence directly testing infection prevention and control advice as related to Gram-negative organisms, particularly MDR strains. A similar lack of evidence was noted in the ESCMID guidelines on preventing transmission of MDR Gram-negative bacteria.[161] Nevertheless, the European Centre for Disease Prevention and Control (ECDC) risk assessment on carbapenemase-producing Enterobacteriaceae showed that there was agreement across Europe that SICPs are an essential integral part of any strategy to control MDR Gram-negative organisms.[168] The supporting European survey of carbapenemase-producing Enterobacteriaceae emphasized the importance of diagnosis, early containment through patient screening and SICPs.[169]

A number of authoritative bodies have produced detailed guidance on carbapenemase-producing Enterobacteriaceae in particular based on expert consensus; these emphasize the importance of continuous implementation of SICPs, with particular emphasis on hand hygiene.[143,162,170,171] PHE, the Centers for Disease Control and Prevention, and ESCMID all recommend contact precautions (patient isolation) in addition to SICPs for all colonized or infected patients with MDR Gram-negative bacteria, as well as those previously colonized and not known to be free of these bacteria.[161,162,170] All patients should be assessed for transmission risk on or before arrival at the care area, and reviewed for any changes in risk during their stay.

In an endemic setting (with constant challenge from admissions of colonized or infected patients), ESCMID does not recommend isolation for ESBL *E. coli*. Other guidance emphasizes basing isolation on a risk assessment while maintaining high levels of hand-hygiene compliance and environmental cleaning.[143] The ST131 clone of *E. coli* appears to be more readily transmissible, and further study is needed.

Other guidelines use general principles based on a range of pathogens. Both National Evidence-Based Guidelines (EPIC 3) and Health Protection Scotland's National Infection Prevention and Control Manual specify good-practice standards based predominantly on expert consensus or Health and Safety legislation, rather than evidence from controlled trials.[166,172]

SICPs include[166,173] the following elements:

- hand hygiene;
- environmental cleanliness, including the decontamination of patient care equipment, the safe management of linen and disposal of healthcare (clinical) waste;
- safe use and disposal of sharps;
- aseptic practice;
- respiratory hygiene; and
- assessment of infection risk, use of personal protective equipment and patient placement.

Contact precautions entail donning personal protective equipment on room entry, and discarding before exiting the patient room. A single room is preferred.[173] Hand hygiene is performed before touching the patient, and prior to wearing gloves for touching the patient and the patient's environment.

Strategies to minimize the transmission of pathogens, including MDR Gram-negative bacteria, will only be successful if there is a reliable high level of compliance with SICPs and contact precautions by all healthcare workers.[174,175] Training, education, audit and feedback are therefore important. Low levels of compliance with hand hygiene and inappropriate glove usage are commonly described.[174,176] Invasive medical devices breach the body's natural defence mechanisms and increase the likelihood of infection and colonization; therefore, device avoidance and minimization are important.

Evidence

Consistent application of SICPs with contact precautions for patients colonized or infected with MDR Gram-negative pathogens reduces transmission. 3

Recommendation

In addition to SICPs, apply contact precautions for those patients who present an infection risk. Strong

Good Practice Recommendation[166]

Apply and maintain SICPs in all care settings, at all times, for all patients.

9.4.2. Screening

9.4.2.1. What is the role of screening in patients and staff?

Early detection of patients colonized or infected with MDR Gram-negative organisms is important for managing their status effectively, and for implementing timely interventions to prevent subsequent spread. Screening of potential colonization sites of patients (e.g. faeces) is essential in limiting the spread of carbapenemase producers in hospitals. Identification of other MDR Enterobacteriaceae is useful to identify those patients who may need carbapenems if treated empirically. Although ESBL *E. coli* are often resistant to ciprofloxacin, the proportion varies widely by country.[26,177,178]

In a multi-centre German study of screening of patients with haematological malignancies, colonization rates with ESBL Enterobacteriaceae varied between 5.3% and 21.8% of patients.[179] In a Korean study of ICU patients, 28% of 347 were found to have ESBL Enterobacteriaceae faecal carriage on admission, and another 12% acquired these organisms during follow-up in ICU. As assessed by pulsed-field gel electrophoresis, none of the acquisitions were nosocomial transmissions, but the methods used would not have readily identified plasmid outbreaks.[180] Routine screening of urine for ESBL *E. coli* and *Klebsiella* spp. followed by single-room isolation of carriers did not result in any significant reduction in the number of ESBL producers isolated from non-urinary sites in hospital.[181] Against the background of a high prevalence of ESBL

Enterobacteriaceae in Korea, routine screening of carriage sites was not cost-effective in ICUs.[180] The risk of dissemination in the local community was high. In Europe, ST131 CTX-M-15 strains are common, but specific screening for that strain has not been studied.

A nationwide intervention in Israel against a clonal outbreak of ST258 *K. pneumoniae* (with a KPC carbapenemase) was successful because it depended on mandatory patient screening and isolation, and patient and staff cohorting.[77] Short- and long-term care facilities were involved, as the latter were a reservoir for re-introduction to acute units. Compliance with national guidelines was reinforced by visits to facilities, reporting of carrier and isolation status, and contact tracing. In high-intensity units such as ICUs, rectal swabs from all the patients on the ward were assessed. Two rectal swabs negative by culture and one rectal swab negative by PCR were required before screening was discontinued for an individual patient in any ward. The programme successfully reduced acquisition of carbapenem-resistant organisms from 55.5 to 4.8 instances per 100,000 patient-days. Screening for non-fermenters such as *Pseudomonas* spp. or *Acinetobacter* spp. is not supported by high-quality evidence, but may be performed in outbreaks (Tables III and IV).

There is usually no indication for screening faecal cultures from healthcare workers or family members, although good personal hygiene should be emphasized. Outbreak investigations that do not identify a single environmental source suggest that transmission is occurring via the hands of hospital staff, but hand cultures are usually negative, presumably because contamination is transient.[182] Gram-negative organisms isolated from nurses' hands are, in most cases, different from those causing significant infections in patients.[13,183] However, outbreak reports are selective and open to bias.

Evidence

Mandatory screening and full implementation of SICPs combined with contact precautions throughout the area of care is effective in controlling clonal outbreaks of carbapenemase-producing pathogens. 2++

Routine screening of carriage sites for ESBL-producing Enterobacteriaceae for infection control purposes may not be cost-effective if community transmission and carriage is frequent. Screening and isolation of carriers of ESBL *Klebsiella* spp. is more likely to be useful than that for ESBL *Enterobacter* spp., *Serratia* spp. or *E. coli*. However, specific screening for specific clones has not been studied. 3

Recommendation

Screening for rectal and wound carriage of carbapenemase-producing Enterobacteriaceae should be undertaken in patients at risk. Strong

Good Practice Recommendation

Routine screening of family contacts and staff is not recommended.

9.4.2.2. What organisms should screening include? Enterobacteriaceae and non-fermenters (i.e. *A. baumannii* and *P. aeruginosa*) constitute the majority of MDR Gram-negative pathogens causing healthcare-acquired infections. Carbapenem-resistant organisms should have priority, as meropenem is currently the most widely used broad-spectrum antibiotic of last resort. Some MDR strains are readily transmissible and require patient isolation. Most carbapenem resistance seen in Enterobacteriaceae, at least among reference laboratory submissions, is now associated with production of KPC, OXA-48, NDM and VIM carbapenemases; almost all carbapenem resistance in *A. baumannii* is associated with OXA-23-, OXA-40-, OXA-51- and OXA-58-related carbapenemases. Carbapenem resistance in *P. aeruginosa* may involve carbapenemase production, but is more commonly related to porin loss, which confers a narrow-spectrum carbapenem-specific resistance profile.

ESBL producers and plasmid or chromosomal AmpC Enterobacteriaceae are resistant to a number of antibiotics, and infection control precautions are used to prevent transmission. A major driver for the use of carbapenems is the suspicion of the presence of ESBL. Screening for ESBL producers may therefore be useful in guiding and thereby limiting empirical use of carbapenem, although no confirmatory reports are available. Where isolation facilities are limited, cephalosporin-resistant Enterobacteriaceae cases and carriers should have a lower priority than patients carrying carbapenem-resistant Enterobacteriaceae. Subject to local risk assessment, colonized patients with diarrhoea or discharging wounds would usually take precedence for single rooms over patients without those characteristics but the same MDR organism.

Recommendation

Screening for carbapenem-resistant *A. baumannii* and MDR *P. aeruginosa* is required in management of outbreaks. Strong

9.4.2.3. Who, how and when to screen patients for multidrug-resistant Gram-negative bacilli?

9.4.2.3.1. Who to screen. The potential risk factors identified for colonization or infection with MDR Gram-negative organisms are similar and wide ranging, and include recent antimicrobial treatment, presence of indwelling devices, severity of illness, admission to an ICU, transfer between hospital units, residence in long-term care facilities, previous surgery, hospital inpatient stay within the preceding year (particularly overseas in an endemic area), recent solid organ or stem cell transplantation, presence of wounds, presence of biliary catheter and mechanical ventilation.[38,161]

Although only limited data are available from studies on interhealthcare transmission of carbapenem-resistant Gram-negative bacteria within countries, a number of descriptive studies indicate that cross-border transfer of patients is associated with a risk of transmission of carbapenem-resistant organisms, particularly in respect of patients coming from the Middle East, India, Pakistan, Italy and Greece.[168] This applies to patients transferred from endemic areas to healthcare facilities in another country, and where patients have received medical care abroad in areas with high rates of carbapenem-resistant organisms. Based on this, a recent ECDC report recommended that all countries should develop guidance for active screening of faeces of all patients transferred from any healthcare facility in an endemic area.[161] Among the first 250 patients in the UK with an isolate producing the NDM carbapenemase, 100 had a travel history, with half of these having travelled to the Indian subcontinent.[184]

Table IV
Infection prevention and surveillance by organism: recommendations by organism/resistance

Recommendation	Application in respect of		
	Resistant Enterobacteriaceae (AmpC, ESBL and carbapenem-resistant organisms)	MDR non-fermenters	
		Acinetobacter baumannii	*Pseudomonas aeruginosa*
1,2. Laboratory test for susceptibility to meropenem for all significant Gram-negative isolates	Test susceptibility to meropenem + cefpodoxime	Test susceptibility to meropenem. Usually confined to ICU	Test susceptibility to meropenem + ceftazidime. Most carbapenem resistance is via loss of OprD, and is less important for infection control than carbapenemases. Carbenicillin and ceftazidime sensitivity indicates OprD loss
3. Request international travel history for patients with carbapenemase-producing Gram-negative bacteria	Find and record	Not usually required — local acquisition	Find and record
4. Diagnostics: detect and report all MDR Gram-negative organisms (at least three resistance mechanisms) in clinical samples and screens in <48 h	Early recognition and infection control intervention to reduce transmission	Early recognition and infection control intervention to reduce transmission	Early recognition and infection control intervention to reduce transmission
5. Active screening rather than monitoring of laboratory reports for high-risk specialities	Case finding/screening for carbapenemase for ICU and other high-risk patients but not routinely recommended for ESBL/AmpC	In outbreaks, case finding/screening for ICU and other high-risk patients. Otherwise, monitor laboratory reports	Poor evidence for screening — may be appropriate in high-risk units (e.g. cystic fibrosis units, burns units, haematology units) or in context of outbreak. Sporadic and epidemic strains co-exist, so tracking of outbreaks may be problematic without typing unless there is a clear phenotype (e.g. metallo-β-lactamase)
6. Risk assessment on admission to ICU and from long-term care facility	Risk assess on admission for carriage of carbapenem-resistant Enterobacteriaceae. ESBLs — not recommended but may be considered on admission from long-stay units	Not recommended on admission except when outbreak in referring ward or hospital	Not recommended on admission except when outbreak in referring ward or hospital
7,8. Screen patients at risk for carbapenem-resistant Enterobacteriaceae	Screen patients assessed as at risk/coming from endemic settings. Screening not recommended for family contacts or staff	Screen in outbreaks. Screening not recommended for family contacts or staff	Screen in outbreaks. Screening not recommended for family contacts or staff
9. Type of sample for screening	Rectal/stool	Skin sites or, if a catheter or endotracheal tube is present, urine, rectal or respiratory secretion	Rectal/stool

10. Screen patients with stay in healthcare facility with endemic carbapenemase-producing organisms in last year	Carbapenem-resistant — targeted screening of patients with history of health care in high-risk areas [i.e endemic, not just sporadic cases (e.g. India, Manchester in UK)]	Carbapenem-resistant — targeted screening of patients with history of health care in high-risk areas (i.e. based on local knowledge of referring centres)	Carbapenem-resistant — targeted screening of patients with history of health care in high-risk areas (i.e. based on local knowledge of referring centres)
11. Monitor SICPs and contact precautions during outbreaks; repeat screening of negative patients weekly and on discharge until no new cases for seven days	Carbapenem-resistant — during outbreak, screen all patient contacts in ward of a new case	Carbapenem-resistant — during outbreak, consider screening all patient contacts in bay/ward of non-isolated case. No evidence for regular admission, ongoing or discharge screening except in outbreaks	No high-quality evidence for patient contact screening, but consider screening all patient contacts in bay/ward in outbreak. No evidence for regular admission, ongoing or discharge screening except in outbreaks
12. At admission, screen patients with previous carbapenem-resistant or other MDR Gram-negative bacteria	Screen all with known previous carriage or infection	Screen all with known previous carriage or infection	Screen all with known previous carriage or infection
13. Contact precautions for patients who present an infection risk	Carbapenem- resistant — pre-emptive isolation of previous positive patients pending screening. Restrict unnecessary patient movements where possible	Carbapenem-resistant — pre-emptive isolation of high-risk patients pending screening. Restrict unnecessary patient movements where possible	No evidence for pre-emptive isolation. Extrapolation from evidence for other MDR organisms suggests that isolation or cohorting of known cases with contact precautions and restrictions on unnecessary movement are appropriate
14. Patients colonized with MDR Gram-negative organisms in single room for duration of stay	No recommendations for tests of clearance — assume long-term carriage during the same inpatient stay	No recommendation for test of clearance	No recommendation for test of clearance
15. Personal protective equipment: use disposable gloves and gown/apron in caring for patients	Apron/gown and gloves for all patient interactions. No requirement for facemasks or respirators	Use apron/gown and gloves for all patient interactions. No requirement for facemasks or respirators	Apron/gown and gloves for all patient interactions. No evidence for the effectiveness of respiratory precautions except for patient-to-patient spread by droplet nuclei in patients with cystic fibrosis
16. Prioritize single-room accommodation (local risk assessment to determine priority against other pathogens, but carbapenem-resistant Enterobacteriaceae usually higher than *Clostridium difficile* or meticillin-resistant *Staphylococcus aureus*)	First priority: carbapenem-resistant Enterobacteriaceae. Carbapenem-resistant Enterobacteriacae: single room, preferably with en-suite facilities, throughout admission. Other MDR Enterobacteriaceae: isolate where possible according to assessment of risk of spread; otherwise, contact precautions	Second priority: carbapenem-resistant *Acinetobacter* spp. These are usually confined to ICU. Carbapenem-resistant: single room, preferably with en-suite facilities, throughout admission. Other MDR *Acinetobacter* spp.: room if available	Third priority: carbapenemase-producing *P. aeruginosa*. Other MDR *Pseudomonas* spp. (e.g. permeability variant): use single room if available
17. Cohort isolate if there are insufficient single rooms	Consider cohorting patients whose isolates have the same phenotypic resistance pattern. Consider staff cohorting where feasible, and education of staff in infection control	Consider cohorting patients whose isolates have the same phenotypic resistance mechanism. Level of evidence for staff cohorting is low	Extrapolation from other infections suggests that staff cohorting may be useful in controlling outbreaks

(*continued on next page*)

Table IV (*continued*)

Recommendation	Application in respect of		
	Resistant Enterobacteriaceae (AmpC, ESBL and carbapenem-resistant organisms)	MDR non-fermenters	
		Acinetobacter baumannii	*Pseudomonas aeruginosa*
18. Hand hygiene before and after direct patient contact	Contact precautions; ensure high awareness of need for attention to hand hygiene, especially with soap and water	Contact precautions and high awareness of need for hand hygiene, especially with soap and water	Low-level evidence. Ensure high awareness of need for attention to hand hygiene, especially with soap and water
19. Environmental screening when unexplained transmission	Persistence in environment in wet areas and respiratory equipment	Environmental persistence, particularly in dust and dry surfaces. Bed rails, bedside tables, hygroscopic bandages, HEPA filters and extract vents implicated	Association with persistently colonized water systems (e.g. taps, filters, aerators, sink traps). Screening of tap outlets in augmented care areas according to local risk assessment. Outbreaks associated with contamination of ventilator equipment
20. Decontaminate equipment in designated cleaning sinks	Indirect evidence for transmission via equipment	Some evidence for transmission through equipment	Evidence for transmission through equipment contamination (e.g. ventilators) demonstrates importance of dedicated and single-use equipment, and decontamination of re-usable equipment by appropriate agents
21. Risk assess point-of-use filters for taps if *P. aeruginosa* colonization/ infection is increasing	Not applicable	Not applicable	Effective in reducing infection but need monthly replacement
22. Terminal disinfection with hypochlorite in outbreak control	Increase cleaning frequency to at least twice daily and every 4 h for high-contact surfaces	Increase cleaning frequency to at least twice daily and every 4 h for high-contact surfaces	Some evidence that cleaning protocols have a role for controlling spread in outbreak settings
23. Consider hydrogen peroxide vapour as adjunct to cleaning	Effective in reducing reservoirs	Effective in reducing reservoirs	Effective in reducing reservoirs on surfaces but not taps or sink traps
24. Routine use of selective digestive decontamination not recommended	Not normally recommended as contrary to antibiotic stewardship	Not recommended	Not normally recommended as contrary to antibiotic stewardship
25. Monitor hand hygiene of all shared staff in cohort isolation	Self-contained nursing unit is effective in control of spread	Self-contained nursing unit is effective in control of spread	No direct evidence

ESBL, extended-spectrum β-lactamase; ICU, intensive care unit; MDR, multi-drug-resistant; SICPs, standard infection control precautions; HEPA, high-efficiency particulate arrestor.

All patients with epidemiological links (same hospital unit or care home) to an index and secondary cases should be screened to determine the extent of secondary transmission. However, carriage may be prolonged in the community (especially in patients with urinary catheters), and the chronology can be difficult to determine. As such, isolation is started on re-admission. Admission screening by rectal swab (or axilla/groin swab for *Acinetobacter* spp.) is required for patients transferred from countries or institutions (including those in the UK) with a prevalence of epidemic or endemic carbapenem-resistant Gram-negative pathogens, as well as those patients with previous colonization or infection. However, that assumes the receiving area (infection control practitioner) has been informed appropriately of prior hospitalization and carriage data, and where endemic or epidemic problems are present.

Given reported prolonged gastrointestinal carriage of MDR Gram-negative organisms, clearance samples are not recommended. Patient isolation should continue for the duration of the inpatient stay unless there is extensive spread and large numbers of colonized or infected patients. Cohorting affected patients together may then be necessary. Colonized or infected patients should be isolated if re-admitted as emergency cases, and should then be screened. Previously colonized or infected patients should be screened as outpatients if admission is planned, and isolated on admission if screening yields the relevant organism. A method of flagging records is needed.[185]

9.4.2.3.2. How to screen. As the intestinal flora is the main source of MDR Gram-negative bacilli (except *Acinetobacter* spp.), a rectal swab (or stool) is preferred for ease of collection, handling and processing,[162,186] but faecal material must be visible on the swab before putting it into transport medium. A stool sample may be used if there is a risk of mucosal trauma. Rectal or perirectal swabs or stool samples have higher yield than testing of other body sites.[116] In patients with indwelling devices, specimens from the related site should be screened. Skin swabs, urine and sputum should be checked in those with chronic wounds, indwelling urinary catheters or endotracheal intubation. *Acinetobacter* spp. are best detected in axillal, groin or wound swabs.[187]

Screening tests should have a turnaround time of less than 48 h. Confirming the specific carbapenemases is important, but requires molecular methods that often limit availability to reference laboratories. Nevertheless, locally performed phenotypic tests can be extremely helpful as the report is available without delay. These tests are easy to implement for most laboratories, provided that the resources are available and laboratory staff have been trained.[162,168] If carbapenemase confirmation is not possible, isolates should be sent to reference laboratories, although infection control precautions should not be delayed. These tests can prove to be even more useful if they are interpreted in conjunction with data on the background prevalence of carbapenem-resistant organisms in a specific region. A rapid diagnostic turnaround time and timely communication of laboratory results to physicians, nurses and the infection control team are extremely important for infection prevention and control and clinical therapy.

Commercial media for detection of carbapenemase-producing Enterobacteriaceae are increasingly available. In a comparison of four chromogenic media used to detect carbapenemase-producing Enterobacteriaceae, chromID Carba had the best sensitivity and specificity, although this may not be adequate for OXA-48.[148] Disc or tablet diffusion synergy tests use meropenem combined with boronic acid to inhibit KPC carbapenemases, or EDTA to inhibit metallo-carbapenemases (IMP, NDM and VIM). Cloxacillin inhibits AmpC but not KPC, facilitating discrimination between isolates with these types of enzyme in an Etest.[143] High-level temocillin and piperacillin/tazobactam resistance without potentiation of meropenem by EDTA is a marker of OXA-48. Molecular confirmation tests show high sensitivity and specificity, and are used in reference laboratories but are expensive and will not detect novel genes. Although several pseudomonas-selective media are marketed, there are no specific data on screening methodology, frequency or duration with respect to *P. aeruginosa*.[161] *P. aeruginosa* resistant to carbapenems but susceptible to other β-lactams can be assumed not to have carbapenemases, and do not warrant reference investigation.

The accuracy of carbapenemase detection may be affected by the species and origin of the pathogen, type of carbapenemase and other resistance properties, such as porin loss or ESBL production. Phenotypic confirmatory tests such as the modified Hodge test are within the capability of most local laboratories, but depressed AmpC enzymes (and sometimes ESBLs) are associated with weak false-positive modified Hodge tests, especially with ertapenem. The test can be difficult to interpret. Colorimetric and MALDI-ToF methods can be used.[188] Some organisms with OXA-48-like carbapenemases only exhibit low-level carbapenem resistance without cephalosporin resistance, thus escaping the standard identification methods.[188]

High sensitivity and specificity in detecting ESBLs can be achieved using chromogenic selective media, despite mixed flora in catheter urine or faeces. However, competitive bacterial flora resistant to multiple antibiotics, especially cephalosporins, can reduce the specificity of selective media. The use of CTX-M Chromagar (CHROMagar, Paris, France) is superior to ESBL chromogenic agars if seeking cases with a CTX-M ESBL in an outbreak, but the medium is less suitable where, for example, TEM 10 ceftazidimase is present.

Screening for carriage of MDR *A. baumannii* has been described using a variety of media with samples from various body sites including axilla, groin, wounds, rectum or pharynx.[104,116,189–192] There is no consensus on site or method of screening for *Acinetobacter* spp., and sensitivity is poor.[193] Most carbapenem resistance involves OXA-23/40/51/58/143-like carbapenemases, whilst a few isolates have metallo-carbapenemase.[194,195]

9.4.2.3.3. When to screen. There is insufficient evidence to mandate routine screening of all patients for colonization by all MDR Gram-negative organisms. However, screening of high-risk patients is used in control efforts for carbapenem-resistant Enterobacteriaceae (e.g. patient transfers from hospitals where these organisms are prevalent). The contribution of this practice to decreasing transmission is unknown. Nevertheless, identifying patients who are at high risk of colonization or infection with MDR organisms (including carbapenem-resistant organisms) and performing screening by rectal swab (or skin for *Acinetobacter* spp.) on admission to healthcare facilities is recommended, and is now becoming more widespread in healthcare settings.[169] Patients at high risk include patients admitted to ICU and from long-term care facilities (e.g. care homes or endemic areas).

Screening for carriage of ESBL Enterobacteriaceae can identify patients in whom empirical treatment with meropenem may be justified, thus supporting antimicrobial stewardship. Discharge screening for ESBL or carbapenem-resistant organisms is appropriate when admission screening is practised, or if a colonized patient is likely to be re-admitted for further procedures or is going to a long-term care facility. Patients with carbapenem-resistant organisms should have notes flagged pending re-admission or if they transfer to long-term care facilities, where there is a risk of further spread. Long-term care facilities should be informed of positive results of discharge screening on their transferees, and may need to consider if their routine SICPs are sufficiently robust for caring for these patients.

Good Practice Recommendations

Effective communications between healthcare settings will help to facilitate efficient patient transfers, and are crucial in reducing spread.

Local screening policies should be developed to define those patients at high risk of carriage of, for example, carbapenemase producers.

9.4.2.4. What can be done in the case of patients unable or unwilling to consent to a rectal swab? On being admitted to hospital, a patient consents to receive those diagnostic and screening tests that are deemed necessary to the management of their presenting problem. In situations where a patient is incapacitated, those giving care may proceed with any interventions deemed necessary to provide medical treatment for the patient's well-being. This follows the principles of 'implied consent' (i.e. it is reasonable to assume that the person would consent if they were not incapacitated and unable to do so). Implied consent is already used for meticillin-resistant *Staphylococcus aureus* (MRSA) screening, even for patients who have the capacity to consent for themselves.

Screening as part of the ward/hospital policy to guide antimicrobial therapy and/or prevent disease transmission does not require specific written consent, but verbal agreement from the patient before sampling is conducted is required whenever possible. Individual, religious and societal concerns have to be respected. Patients should be informed, whenever possible, of the need and reason for screening (i.e. that it is for their benefit and that of other patients, and what it involves). They should be given the option of who carries it out, including self-screening, but only after assessment of their ability and willingness to comply, and safety of the procedure. The option of a same-sex healthcare practitioner should be provided. Some patients may be unwilling to accept a rectal swab but will provide a stool sample, although this may result in delay or absence of a sample. Ideally, patients should be placed pre-emptively in an isolation room while the screening results are awaited, but this is unlikely to be practicable in many high turnover wards. Patients having chemotherapy or with an underlying bowel condition (stoma, colon cancer, recent anal or rectal surgery) may be more easily screened using stool. Nevertheless, rectal swabs can be collected safely in haematology patients.[196]

9.4.2.5. How frequently does screening need to be performed? Extensive active screening during outbreaks due to carbapenem-resistant organisms is recommended[168] (e.g. follow-up screening of negative cases at weekly intervals and/or for all inpatient contacts with confirmed cases). Although such accounts must be interpreted with caution, experience from outbreaks of MDR Gram-negative organisms, including carbapenemase- and ESBL-producing Enterobacteriaceae, in acute healthcare settings suggests that the implementation of screening for early detection and isolation of colonized patients coupled with contact precautions can help to control transmission.[77,169,197] Screening of those not known to be carriers of carbapenem-resistant organisms in an endemic situation is advisable at least weekly and on discharge.

9.4.2.6. Is there evidence for effective interventions on positive patients (i.e. can carriage be cleared)? A number of studies have evaluated the duration of colonization with MDR Gram-negative bacteria. Studies of hospital inpatients suggest that they tend to remain colonized for the duration of their stay.[104,198–200] Most studies evaluating the duration of colonization outside of acute settings for a range of MDR Gram-negative bacteria have identified mean durations of colonization of months rather than days.[11,201–204] This duration is likely to reflect the particular strain, not its resistance.

Several studies have investigated the duration of colonization with carbapenem-resistant Enterobacteriaceae following discharge from acute care facilities. Risk factors for prolonged carriage of MDR Gram-negative bacteria tend to be associated with healthcare contact, underlying medical conditions and the presence of invasive devices.[11,47,199,205] For example, Lubbert *et al.* evaluated prolonged colonization following an outbreak of carbapenem-resistant *K. pneumoniae* following discharge from an acute hospital.[205] Although 26 (31%) of the 84 patients included tested negative for carbapenem-resistant *K. pneumoniae* at one month post discharge, 45% remained colonized at six months and one patient remained positive for almost 40 months. Two other studies found that approximately half of patients colonized at the time of hospital discharge were spontaneously free by six months.[11,47] However, a number of studies identified patients who retested positive after negative screens, suggesting that gastrointestinal colonization is suppressed rather than eliminated in many cases.[47,205] For this reason, the authors of these studies recommend at least three consecutive negative screens separated by at least 24 h before a patient can be considered 'decolonized'.[47,200,205] In practice, colonized inpatients should be considered 'carriers' during the rest of their hospital admission. The risk period from previous hospitalization exceeds one year.

There is no effective equivalent of the topical suppression used to reduce shedding of MRSA in the healthcare environment. Attempts at eradication of MDR Gram-negative organisms from the gastrointestinal tract have not been successful.[206–209] Selective decontamination of the digestive tract (SDD) can produce some temporary reduction in the number of organisms in faeces (see Section 9.4.6).

Evidence-based criteria for discontinuing contact precautions for carbapenem-resistant Gram-negative organisms in acute care settings have not been developed. Given the likelihood for prolonged gastrointestinal carriage by these organisms and risk of spread, organizations should be cautious in discontinuing contact precautions (patient isolation). In most cases, contact precautions should continue for the duration of the hospitalization

during which the organism was first found on culture. Patients re-admitted within 12 months of that hospitalization should be considered probably colonized, and managed with contact precautions until at least one negative screen is available.

Evidence

Early recognition of patients infected with MDR Gram-negative organisms and implementation of rigorous infection control interventions is usually associated with reduced secondary transmission. 3

Screening (except *Acinetobacter* spp.) is most sensitive when performed on rectal (or perirectal) swabs or stool specimens. 3

Patients transferred from, or who have received medical care in, a healthcare facility in an endemic area of the UK or abroad are at high risk of carriage of carbapenemase-resistant organisms. 2++

Recommendations

A rectal swab (with visible material) or stool sample (and urine sample if catheter present) should be used for screening for multi-resistant Enterobacteriaceae and *P. aeruginosa*. For *Acinetobacter* spp., sample skin sites or (if a catheter or endotracheal tube is present) urine or respiratory secretions. Conditional

Each healthcare organization should have access to robust microbiological arrangements for detecting and reporting MDR Gram-negative organisms in routine clinical samples, and for screening using highly-sensitive tests with a rapid diagnostic turnaround time of $<$48 h. Conditional

All patients transferred from, or with a history in the preceding year of admission to, healthcare facilities with known endemic carbapenemase-producing Enterobacteriaceae should be screened. Strong

In the event of secondary cases of carbapenem-resistant Enterobacteriaceae, SICPs and contact precautions should be monitored and re-inforced with clinical staff. Screening of patients not identified as carriers should be repeated weekly and on discharge from affected units until no new cases are identified for more than seven days. Strong

Where possible, single-room isolation should be provided for patients with MDR Gram-negative bacterial infection/colonization, and contact precautions should be continued for the duration of their stay. Conditional

Patients with previous samples with carbapenem-resistant or other MDR Gram-negative bacteria should be screened at the time of admission. Conditional

9.4.3. Isolation and segregation

A long-standing principle of infection prevention and control is to physically segregate those known to be infected or colonized with a pathogen of epidemiological importance from those who are not infected or colonized. However, critical appraisal is difficult as segregation is usually assessed as part of a package of measures. This physical separation can be achieved through placing patients with known/suspected infection/colonization in single rooms; and/or identifying and isolating patients with the same, confirmed pathogen in a cohort room/area. An additional cohort measure (nursing staff numbers permitting) is to identify staff to care for those patients placed in cohorts. The implementation of screening cultures at the time of admission or during a patient's stay on a particular ward is a way to improve the impact of physical segregation by identifying those who are colonized with the pathogen of concern.

Placing patients known to be infected or colonized with MDR Gram-negative bacteria in single rooms reduces transmission. Several studies have reported the impact of converting a unit from multi-occupancy to single rooms on rates of MDR Gram-negative infection/colonization.[210–214] A Canadian study reported the acquisition rate ratio of various Gram-negative bacteria, comparing an intervention unit that had been converted into single rooms with a control unit in a sister hospital that had not been converted into single rooms.[210] The number of *Acinetobacter* spp., *Klebsiella* spp. and *Enterobacter* spp. fell significantly, but the number of *Pseudomonas* spp. and *E. coli* did not. A 20-year before–after study from a US burns ICU that was converted into single rooms reported a significant reduction in Gram-negative bacteraemia, the time to a first positive Gram-negative culture and mortality.[212] Significant reductions were also reported in bloodstream infections due to *P. aeruginosa*, *K. pneumoniae*, *E. cloacae*, *E. coli* and *Providencia stuartii*. However, there was no control unit, and improvements in burns care during the study may have contributed to these reductions. A separate study from the same renovation reported an overall reduction in infection rates, mortality and non-enteric Gram-negative species.[213] One study from a US ICU reported no significant reduction in overall infection rates, or in rates of *E. coli*, *Pseudomonas* spp., *Acinetobacter* spp., *Klebsiella* spp. or *Serratia* spp.[211] Again, this study did not include a control ward. Hand hygiene compliance was low and did not increase when the unit was converted into single rooms, in contrast to other studies.[215,216]

The impact of enhancing patient isolation aside from other interventions has been evaluated. A French study in 2001 found that introducing patient isolation to care for ESBL carriers resulted in a sequential reduction in ESBL incidence and hospital acquisition.[217] However, this preceded the emergence of CTX-M and *E. coli* as dominant factors. A study in a Vietnamese ICU found that improving patient isolation by re-inforcing hand hygiene, and limiting exchange of equipment, materials and staff between patients did not reduce exogenous transmission of various Gram-negative bacteria (gentamicin-resistant *K. pneumoniae*, ESBL Enterobacteriaceae, amikacin-resistant *Acinetobacter* spp. and *P. aeruginosa*), whereas rates of MRSA fell significantly. However, this study did not include physical segregation of patients or the use of gowns or aprons.[218]

Various studies have evaluated switching from a multi-occupancy ward to a single-occupancy ward. An Israeli study showed that there were significantly fewer acquisitions of resistant organisms when an ICU was converted from a multi-occupancy bay to single rooms.[215] The study included a control ward which had not been converted. Patients in the single-room ICU had a significantly lower acquisition rate of resistant organisms when compared with the control multi-occupancy ICU over the same period [3/62 (5%) vs 7/39 (18%), respectively, $P = 0.043$]. SICPs were applied throughout, but compliance with hand hygiene was better in the single-room ICU. Although MDR Gram-negative organisms were included, the significant changes related to Gram-positive pathogens. Another study found that the mean number of nosocomial infections and length of stay were reduced significantly when a multi-occupancy paediatric ICU

was converted to single occupancy.[219] However, no control ward was used, and no specific data on MDR Gram-negative pathogens were reported.

Although these studies suggest that converting multi-occupancy wards to single rooms reduces the spread of MDR Gram-negative pathogens, there are several limitations. First, most studies did not include a control ward (although both of the studies that included a control ward found a significant reduction in transmission).[210,215] Second, compliance with hand hygiene is higher in a single-room format compared with a multi-occupancy setting.[215,216] Thus, it could be that improved hand hygiene rather than improved physical segregation is the critical factor for reducing transmission. All of the studies were performed in an ICU setting, limiting their applicability to settings outside of critical care. Converting wards to single rooms often includes other changes, such as the size of each bedspace, and the location and number of hand hygiene facilities, which could influence transmission rates.[215] Single rooms are associated with a number of drawbacks, particularly an increased risk of adverse events due to reduced observation and psychological effects, so the requirement for patient observation is a key consideration when deciding on the optimal configuration of wards.[220] Finally, patients are increasingly moved around the hospital for procedures and investigations, challenging their segregation.

9.4.3.1. Cohorting staff. No studies have evaluated the impact of cohorting staff aside from other interventions, but several studies have reported cohorting staff as an element of a successful multi-faceted strategy.[77,104,221,222]

9.4.3.2. Disposable aprons and gloves. Data are limited in terms of the most appropriate personal protective equipment to use when caring for patients with MDR Gram-negative bacteria.

Studies have evaluated interventions that have included the use of gloves and gowns or aprons as an element of contact precautions.[137,217,223,224] Hands and uniforms (or gloves and gowns or aprons if worn) can become contaminated with MDR organisms.[126,127,225–230]

The use of gloves is an essential part of prevention of transmission of infection, and the evidence has been reviewed elsewhere.[176] While they protect hands from contamination with biological fluids and micro-organisms, gloves are not a substitute for hand hygiene, and unnecessary use can result in increased cross-contamination. Loveday *et al.* recommended that gloves should be removed immediately after the activity has been completed, and the hands then decontaminated to prevent transmission as they may be contaminated during glove use or during removal.[176]

Evidence

Units composed of single rooms have less transmission of MDR Gram-negative bacteria: *A. baumannii*, ESBL-producing (and, by inference, carbapenemase-producing) Enterobacteriaceae, *P. aeruginosa*. 3

Recommendation

Use disposable gloves and gowns or aprons to care for patients with MDR Gram-negative bacteria: *A. baumannii*, carbapenem-resistant and ESBL Enterobacteriaceae, *P. aeruginosa*. Strong

9.4.3.3. What is the role of isolation in care home/hospital settings? Current practices for the identification and isolation of patients with MDR Gram-negative bacteria (in either single rooms or cohorts) vary widely among healthcare facilities.[231,232] A survey of 66 hospitals in 26 US states and 15 other countries found that 74.2% isolated patients with ESBLs, 93.9% isolated patients with carbapenem-resistant organisms, 81.8% isolated patients with MDR *Pseudomonas* spp. and 84.9% isolated patients with MDR *Acinetobacter* spp. There was considerable variation in the duration of isolation, and few facilities performed screening. Isolation of patients in long-term care facility rooms may not be practicable for psychological reasons.

A number of studies have evaluated the impact of isolating patients with ESBL Enterobacteriaceae aside from other interventions.[217,233–236] A six-year Canadian study evaluated the impact of placing patients with ESBL Enterobacteriaceae in single rooms for the duration of their stay, and applying contact precautions for symptomatic patients.[233] There was an overall increase in ESBL Enterobacteriaceae colonization/infection, but a relative decrease in cases attributable to the hospital, suggesting that local transmission was reduced. A 2-year before–after study in France before the proliferation of CTX-M β-lactamases found that the introduction of admission and weekly surveillance combined with isolation of carriers resulted in a significant reduction in the percentage of patients infected or colonized with ESBL Enterobacteriaceae.[234] There was a significant reduction in ESBL-producing *K. pneumoniae* but not MDR *E. aerogenes*. The study has a number of important confounders, including an intervention to reduce the use of imipenem, encouraging prompt discharge and chlorhexidine bathing for isolated patients. A study in a French paediatric hospital evaluated a sequential change in isolation policy from placing patients in a single room to placing them in a cohort block, applying modelling to test the impact on transmission of ESBL producers.[235] No significant difference was identified between the two isolation protocols, but the model suggested that single-room or cohort isolation reduced transmission of ESBL producers. Finally, a 12-month cluster randomized study in 13 European ICUs evaluated chromogenic agar screening for ESBL Enterobacteriaceae on admission and isolation of carriers vs no admission screening.[236] A hand hygiene improvement programme for staff and chlorhexidine body washing for patients preceded the trial. Of the 2129 Enterobacteriaceae resistant to third- and fourth-generation cephalosporins found on screening, 29% were resistant to carbapenems. Screening and source isolation was not associated with any trend (during the intervention period) or step change (compared with a baseline period) in rate of ESBL transmission. However, individual species were not analysed separately.

Two studies have evaluated the impact of isolation on the transmission of *A. baumannii* and *P. aeruginosa*.[137,223] A seven-year before–after study in France evaluated the introduction of hospital-wide contact precautions, which included placing the patient in a single room or cohort with other patients, and the use of gloves and gowns or aprons, on the transmission of *A. baumannii*.[223] Isolation precautions were implemented for two years, then stopped for three years, then re-implemented for two years; the incidence of *A. baumannii* was significantly lower during the two periods when isolation precautions were in use. The implementation of isolation precautions was the only variable associated with lower incidence of *A. baumannii*

in multi-variate analysis. A follow-up study from the same group reported similar findings.[237] A study from an ICU in Brazil evaluated the introduction of contact isolation, including the use of gloves and gowns or aprons, cohorting of medical items (stethoscopes etc.), daily surface cleaning and disinfection on the rates of MDR *A. baumannii* and *P. aeruginosa*.[137] Bloodstream infections reduced significantly during the intervention, but species were not analysed separately. The study compared rates of infection at two points during the intervention, with no baseline period.

A number of other studies have implemented complex interventions that included increased isolation of patients.[116,221,222,224,238] One study in a US ICU implemented a multi-faceted intervention centred on improved isolation of patients, including admission screening for carbapenem-resistant *K. pneumoniae* but not for *A. baumannii* or *P. aeruginosa*.[221] There was a significant reduction in the rate of carbapenem-resistant *K. pneumoniae,* but no change in the rate of *A. baumannii* or *P. aeruginosa*. A study of various interventions in six US hospitals found that the only consistent predictor of successful control of *K. pneumoniae* with KPC carbapenemases was a shorter length of stay.[238] Three studies have evaluated the impact of a multi-faceted intervention to control the spread of *A. baumannii*. An intervention at US field hospitals in Iraq including improved hand hygiene, contact precautions, and cohorting patients and staff resulted in a significant reduction in *A. baumannii* ventilator-associated pneumonia.[222] A bundle of interventions including contact precautions, screening (on occasion) and regular staff briefings reduced the rate of MDR *A. baumannii* infections significantly overall, particularly bloodstream infections due to the organisms, in a Spanish hospital.[116] Finally, a study in a Thai ICU reported a significant reduction in MDR *A. baumannii* associated with the introduction of contact precautions, cohorting colonized patients, screening and environmental disinfection using bleach.[224] However, acinetobacter infections are more common in Thailand than in the UK.

Studies that have evaluated the impact of isolating patients in either single rooms or cohorts generally lack a concurrent control unit, making it difficult to be certain that changes in rate are attributable to isolation alone. The one study that included a concurrent control ward demonstrated no significant decrease in transmission of ESBL-producing Enterobacteriaceae.[236]

Evidence

Transmission of MDR Gram-negative bacteria is reduced by identifying patients who are infected or colonized, and placing them in single rooms or cohorts. 3

Recommendations

Identify and place infected and colonized patients in single rooms where available in this order of priority: carbapenem-resistant Enterobacteriaceae, carbapenem-resistant *A. baumannii,* ESBL *Klebsiella* spp., carbapenemase-producing *P. aeruginosa*, ESBL *E. coli* and other Enterobacteriaceae, AmpC Enterobacteriaceae. Strong

If insufficient rooms are available, cohort isolate following local risk assessment. Conditional

Good Practice Recommendation

Establish a flagging system for patient notes. Conditional

9.4.4. Hand hygiene

Hand hygiene is an essential part of prevention of transmission of infection in health care, and it has been reviewed by Loveday *et al.*[176] Transient flora, including MDR Gram-negative bacteria, is acquired from touching the patient or environment, and is easily transferred to the next patient or surface. In turn, this causes colonization and later (potentially) infection. Use of alcohol hand rub (or liquid soap and water if hands are visibly soiled) has been shown to reduce the carriage of potential pathogens on the hands, and therefore is likely to reduce the number and likelihood of healthcare-associated infections.[174,176] Hand decontamination is considered to have a high impact on outcomes that are important to patients.[239] Training of all care workers, combined with audit and feedback of compliance rates, is central to current guidance on prevention of infection. The WHO Five Moments for Hand Hygiene has been widely used and supported by NICE, and describes the points at which hand hygiene is required.[239] Hand hygiene is often missed as the worker enters or leaves the patient environment, and on contact with potentially contaminated surfaces[240–242]

Despite many activities around the improvement of hand hygiene products, the introduction of alcohol-based hand rubs/gel, improving environmental factors, and extensive marketing and education campaigns, evidence of sustained compliance improvement is lacking. Globally, hand hygiene compliance is variable, with Creedon[243] and Larson *et al.*[244] suggesting a rate of approximately 50%. Therefore, improving compliance with hand hygiene is reliant upon an understanding of the interactions within health care between the individuals, the practices and procedures they perform, the environment that they work in, and the culture and safety awareness of the organization. These human factors should be applied to the infection prevention agenda to ensure that meaningful, sustainable interventions are adopted reliably to produce the greatest impact.[245]

Evidence

Hand hygiene is associated with reduction of carriage of potential pathogens on the hands. 2+

Recommendation

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. Strong

9.4.5. Environmental hygiene

9.4.5.1. When should the environment be sampled? The role of the environment in the transmission of healthcare-associated infection remains controversial and difficult to study. In recent years, much of the research around this has focused on high-profile Gram-positive pathogens such as MRSA, *Clostridium difficile* and glycopeptide-resistant enterococci, where a significant body of evidence for the importance of environmental sources has started to accumulate.[246,247] Reservoirs can be identified when infection control has failed to control an outbreak.[161] The general view has been that Gram-negative bacteria, particularly members of the Enterobacteriaceae, are not as successful at surviving in the environment for prolonged periods, and generally are relatively easily removed by

appropriate conventional cleaning and drying.[13] Nevertheless, Enterobacteriaceae, including carbapenem-resistant strains, are able to survive on dry surfaces for extended periods, sometimes measured in weeks and months.[248,249] Some strains of *E. coli* carrying ESBLs, for example, can survive for a median of 10 days in the environment.[250] In favourable conditions, *E. coli, Klebsiella* spp. and *Pseudomonas* spp. can survive for even longer.[161] *Acinetobacter* spp. have the capacity for long-term survival on dry surfaces.[14,251,252,253] *Pseudomonas* spp. are more traditionally associated with moist environments, and will be found around handwash basins and respiratory equipment.[35,254] There is considerable evidence that *P. aeruginosa* can contaminate waste water systems and spread from them, with these sometimes acting as reservoirs for carbapenemase-producing strains causing prolonged outbreaks.[255] If not adequately decontaminated (including the hand piece), endoscopes have been found to be responsible for outbreaks.[256]

MDR Gram-negative bacteria, including carbapenem-resistant organisms, Enterobacteriaceae and *A. baumannii*, can be cultured from sites surrounding infected and/or colonized patients.[106,257] Several studies have found that environmental contamination with resistant *K. pneumoniae* is more common than contamination with resistant *E. coli*.[258–260] No controlled studies have shown that an environmental intervention reduces the transmission of MDR Gram-negative rods. However, contamination with MDR Gram-negative bacteria can persist despite cleaning and disinfection.[106,261,262] Epidemiological data suggest that admission to an ICU room previously occupied by patients infected or colonized with *A. baumannii* or *P. aeruginosa* presents an increased risk for acquiring these organisms.[252] A significant correlation was noted between the number of environmental swabs in monthly screening and the number of patients with colonization/infection in the same month ($P = 0.004$).[103] However, this association was not seen for resistant Enterobacteriaceae, suggesting that the environment is less important in their transmission,[252,263] albeit with the caveat that these studies did not stratify by Enterobacteriaceae spp., which may be important given the increased capacity for *K. pneumoniae*, in particular, to contaminate and survive on hospital surfaces.

The evidence for the benefit of environmental screening is limited, and environmental sampling, in itself, will not limit transmission of MDR Gram-negative bacteria.[264] The purpose of screening may be to draw attention to failure of clearance of an outbreak strain by cleaning, or to point to a possible common source for a cluster or outbreak. Most of the evidence surrounding environmental screening is within reports of management of outbreaks, and there is often very little detail on sites sampled, sampling technique or method of culture.[265] When looking for small numbers of organisms or bacteria living in biofilms, the yield can be improved by using enriched culture, but this precludes quantitation. An alternative to specifically seeking the MDR outbreak strain(s) itself is to assess the degree of microbiological contamination by using surface contact plates and undertaking quantitative bacterial culture.[266] Surface contact plates using selective media for specific pathogens can suffer from low sensitivity, but use with non-selective media may be helpful. Choosing sites for sampling remains problematic as any sampling can only reflect a very small fraction of the relevant environment.[267] The general approach should be to choose sites that are likely to be relevant for cross-transmission, such as work surfaces close to the patient and equipment/surfaces that are likely to be touched frequently (e.g. computer keyboards, bed rails and door handles).[264,268]

Given the difficulties with microbiological sampling of the environment, there has been considerable interest in the availability of technologies that can indirectly assess microbial contamination. Adenosine triphosphate (ATP) bioluminescence has been used for many years in the food industry, where visual assessment is considered to be insufficient to assess the risk of infection from contaminated surfaces. It has a number of potential benefits, including simplicity and immediacy of feedback; however, it can give only indirect information on the likelihood of bacterial contamination, and bacteria themselves are not isolated for investigation and comparison with those causing outbreaks. Its use in hospitals can be problematic, as values can be variable and there is little consensus on an appropriate benchmark value to indicate inadequate cleanliness.[166,269,270] Results are prone to interference by different disinfectants.[271] Where ATP bioluminescence has been used most successfully has been on a continuous basis to improve compliance through feedback and improved cleaning.[272,273] Other methods of controlling the process of cleaning, such as the use of fluorescent gel markers, can be useful in auditing the cleaning process and feedback to cleaning staff.[274]

Evidence

Transmission of MDR Gram-negative bacteria, particularly non-fermenters, has been associated with contamination of the environment, water systems or equipment. 2–

Sampling of the environment can be useful in identifying sources of ongoing transmission or a single common source for an outbreak. 2–

Recommendation

Environmental screening should be considered where there is any unexplained transmission of MDR Gram-negative organisms or a possible common source for an outbreak. Strong

9.4.5.2. What is the evidence that respiratory equipment contributes to transmission? The respiratory tract of ventilated patients in critical care units is a frequent site of carriage of MDR Gram-negative bacteria. In one study in India, 87% of samples from ventilators, humidifiers, nebulizers and other respiratory equipment showed bacterial colonization, and 17/42 Gram-negative isolates were multi-drug resistant.[275] Endotracheal suctioning is a potential cause of cross-infection, as disconnection of the system may allow airborne spread to the patient's skin, staff hands and the immediate environment. In a crossover study in the Netherlands, there was no significant difference in acquisition of Gram-negative bacteria during periods of using closed suction vs open suction in ventilated patients.[276] However, antibiotic resistance rates were low and similar in each group. Comparing ventilated with non-ventilated patients in the ICU, non-fermenting and enteric Gram-negative bacilli were reported more frequently in ventilator-associated pneumonia, but this reflected the number of samples cultured per patient. The overall proportions of different pathogenic species were similar.[277]

Inappropriate washing of ventilator or endotracheal tubing in handwash sinks risks the spread of Gram-negative pathogens. Environmental sampling in two outbreaks of MDR *P. aeruginosa* showed it to have colonized the waste

water system, with blockages, splashback and spillage from showers being possible modes of spread.[35] Direction of water directly into the outlet caused spread of organisms from the sink drain trap. Sinks were fitted with a horizontal drain outlet at the back of the basin, resolving the problem. Sterile fluids (not tap water) must be used to clear suction equipment, as the latter may be contaminated with pseudomonads or Enterobacteriaceae, and these can be disseminated when the equipment is next used, including when catheters are changed.

Evidence

Gram-negative bacteria colonize respiratory equipment and may be washed into sink traps. 2+

Recommendation

Respiratory and other contaminated equipment should be decontaminated (or respiratory secretions discarded) away from the immediate bed area in designated cleaning sinks and not in handwash sinks. Strong

Good Practice Recommendation

Do not discard patient wash water, body fluids, secretions or exudates into handwash basins.

9.4.5.3. What is the evidence that sensor taps contribute to transmission? P. aeruginosa, including MDR strains, in water sources in ICUs has long been recognized as being associated with the development of bacteraemia and pneumonia in patients.[278] A recent systematic review demonstrated evidence of transmission of *P. aeruginosa* from water systems to patients and vice versa.[34] Point-of-use filters and increasing chlorine disinfection were effective interventions. Non-touch taps were identified as probable risk factors for biofilm formation and subsequent transmission to patients. Sinks and nurses' hands have been identified as possible vectors. In a neonatal unit, four neonates were infected and 44 were colonized by cross-infection with one clone.[124] In another neonatal unit in Germany, *P. aeruginosa* was isolated from the nasal prongs of 22 babies and from nine respiratory water reservoirs.[279] The hands of staff were the likely means of transmission. Other outbreaks have been due to contaminated detergent-disinfectant solution used in cleaning surfaces.[280] Studies have confirmed the effectiveness of point-of-use filters on water outlets in reducing infection in critical care units, but as they were descriptive cohort studies, they were subject to temporal variation.[281–283] Filters have to be replaced regularly, are expensive and can themselves be the source of contamination. *P. aeruginosa* is found in biofilm in flow straighteners, metal support collars and the adjacent parts of tap bodies. The level of contamination with *Pseudomonas* spp. is highest on complex flow straighteners, integrated mixers and solenoids.[278]

Sensor taps have been implicated in some outbreaks of pseudomonas bacteraemia and other infections in augmented care units as the flow is slow and controlled, and the internal mechanism is complex. Decontamination of sensor taps can be performed[284] and, in one major outbreak, all taps, mixer valves, flexible hoses and flow straighteners were replaced with simpler designs.[278]

Where there are vulnerable patients (i.e. augmented care), the Department of Health in England recommends a regular water-testing regimen; clinical surveillance is sufficient elsewhere. The frequency of testing depends on previous isolation of the organism and proximity to patients at risk (e.g. neonates). The purpose is to prevent colonization before the development of infection. A risk assessment to mitigate risks and a water safety plan are advised, including consideration of removal of thermostatic mixer valves and flow straighteners, and the design of the sink.[36] Infrequently-used taps should be flushed at full flow for 1 min daily or removed altogether. In the event of contaminated supplies, sterile water should be used for neonates, and single-use wipes should be used for other patient hygiene together with additional hand hygiene using alcohol gel after washing.

Evidence

The presence of infections with *P. aeruginosa* in patients is commonly associated with isolation of these bacteria from unit taps. 2–

The installation of point-of-use filters is associated with a reduction in pseudomonal infections. 3

Recommendation

For *P. aeruginosa*, including MDR strains, at a minimum in accordance with the organization's water safety plan, a risk assessment should be made when levels of patient colonization or infection rise, in order to determine if point-of-use filters should be installed or taps changed. Strong

9.4.5.4. Is any cleaning method more effective than others at removing multi-drug-resistant Gram-negative bacilli from the environment? The importance of persistence of transmission of MDR Gram-negative bacteria in the environment remains uncertain.[246,285] However, maintaining a clean environment and appropriately decontaminating all relevant equipment is an essential component of any infection prevention and control programme. The cleanliness of healthcare premises is an important component in the provision of clean safe care.[286] In England, the NHS Constitution pledges 'The NHS commits to ensure that services are provided in a clean and safe environment that is fit for purpose, based on national best practice'.[287] Whilst there have been significant improvements in the cleanliness of English healthcare premises, there is still room for improvement.[286]

The optimal methods for cleaning have been poorly studied with respect to MDR Gram-negative bacteria. Poor cleaning practice, such as inappropriate dilution of cleaning agent or inactivation of disinfectant by organic matter, is more likely to reduce cleaning efficacy than theoretical cross-resistance between disinfectant and antibiotic.[288] In extreme cases, agents used for cleaning can even become contaminated with Gram-negative bacteria, especially pseudomonads.[141,289–291]

Conventional decontamination is carried out by a human operator, and the reliance on the operator to select the correct product, dilution, distribution and surface contact time has the potential for decontamination failure. Debate around the use of chemical disinfectants vs detergents for routine cleaning is gathering momentum with concerns regarding chemical resistance, optimum disinfectant contact times, allergies amongst users and patients, and costs. In short, practice varies widely and monitoring is traditionally by visual inspection, which can be subjective. Efficacy is rarely measured.

Although persistence of Gram-negative organisms on reusable bedpans is a potential mode of spread, there are no

recent reviews of performance with respect to Gram-negative bacteria. In automated washer disinfectors, a combination of alkaline detergent and temperature over 85°C for 1 min is sufficient to eliminate *C. difficile* spores.[292] However, visible faecal soil can remain on 7–33% of bedpans, so appropriate education is important to ensure good practice.[293] Early studies showed that failure to attain 80°C was associated with persistence of *E. coli* and *P. aeruginosa*.[294] Transmission of pathogens via contaminated endoscopes is usually due to failure to comply with appropriate reprocessing practice guidelines.[295] Although some cases of transmission have been known, relatively few have been reported in peer-reviewed journals.

Assessment of the activity of disinfectants against MDR Gram-negative bacteria is hampered by the differences between testing against organisms in suspension and on a surface. *Acinetobacter* spp. and *Pseudomonas* spp. may survive in the ward environment even after bleach disinfection, and increase the risk of acquisition by patients.[106,252] In a prospective cohort study, cleaning the environment with sodium hypochlorite instead of detergent-disinfectant plus chlorhexidine bathing of patients reduced the risk of colonization with MDR *A. baumannii* becoming established beyond that achieved by improved contact precautions, cohorting, screening and antimicrobial stewardship.[296] Termination of acinetobacter outbreaks has been associated with closure and cleaning of units, and removal of a reservoir has been associated with termination of outbreaks for a variety of organisms.[161]

Most interventions to improve cleaning have been accompanied by a package of infection control precautions. Education campaigns and use of audit tools such as marking surfaces with fluorescent dye reduce contamination, but their effect may be transient.

Recently, there has been significant interest in the role of 'no-touch' automated disinfection systems as an additional measure for terminal cleaning of single rooms or hospital areas affected by clusters or outbreaks.[297] Various types of systems are currently marketed, including aerosolized or vapourized hydrogen peroxide, and ultraviolet radiation. Each has distinct microbiological and practical characteristics. A number of studies have shown improved efficacy of killing of various pathogens compared with cleaning alone, particularly in outbreaks, but there are limited data on whether this reduces acquisition rates of pathogens.[298–300] Hydrogen peroxide vapour from 30% H_2O_2 and, in one case, aerosolized hydrogen peroxide from 5% H_2O_2 have been used successfully as part of a bundle of interventions to prevent transmission of MDR *Acinetobacter* spp. in outbreaks,[105,107–109] and hydrogen peroxide vapour has been used to help control outbreaks of resistant Enterobacteriaceae, including those resistant to carbapenems.[262,301,302]

Patients admitted to rooms exposed to hydrogen peroxide vapour were significantly less likely to acquire any MDR organisms than patients admitted to rooms that had not been treated with hydrogen peroxide vapour in a cohort intervention study.[299] *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* in suspension are all susceptible to low concentrations of hydrogen peroxide, but efficacy is significantly reduced when the organisms are in biofilm; some *P. aeruginosa* in biofilm had prolonged survival following hydrogen peroxide exposure in the laboratory.[303] Hydrogen peroxide vapour (from 30% H_2O_2) is more effective in eradicating surface *A. baumannii* than aerosolized hydrogen peroxide (from 5% H_2O_2) (>6 log vs 1-4 log reduction).[304] It is essential to ensure that the area has been thoroughly cleaned first, because efficacy is affected by the presence of organic soiling.

Evidence

Cleaning is important in the control of outbreaks due to MDR *Acinetobacter* spp., and failure to clean specific areas or pieces of equipment has been associated with transmission of other MDR Gram-negative bacteria. However, evidence derived from before–after studies and outbreak reports is open to bias. 2–

Hydrogen peroxide vapour is effective in reducing environmental reservoirs of *Acinetobacter* spp. and other Gram-negative bacteria on surfaces (but not sink traps) if used in addition to standard cleaning. 2+

Recommendations

Terminal disinfection of vacated areas with hypochlorite should be used in the control of outbreaks of MDR Gram-negative infection. Conditional

Hydrogen peroxide vapour should be considered as an adjunctive measure to follow cleaning of vacated isolation rooms/areas. Conditional

Good Practice Recommendation

Increase cleaning frequency to at least twice daily, and every 4 h for high-contact surfaces in the presence of resistant Enterobacteriaece and *Acinetobacter* spp.

9.4.6. Selective decontamination: why is it not used? Is there a role?

SDD is an intervention that aims to reduce mortality and morbidity due to healthcare-associated infection in ICUs. It comprises application of non-absorbable antibiotics to the mouth and stomach together with a course of broad-spectrum intravenous antibiotic(s). A modification uses only the topical element of decontamination [selective oropharyngeal decontamination (SOD)]. The practice has been investigated extensively, largely in the Netherlands, and at least 12 meta-analyses of published papers have been produced.[305] Almost one-third of the trials suggest a significant reduction in the incidence of Gram-negative pneumonia, and one large randomized study demonstrated a small but significant reduction in mortality in a country with low levels of antibiotic resistance.[306] Despite issues with blinding, heterogeneity and compliance, both SDD and SOD appear to be associated with a reduction in pneumonia (OR 0.32, 95% CI 0.26–0.38) and mortality (OR 0.75, 95% CI 0.65–0.87).[307]

Nevertheless, only 5% of UK ICUs use SDD, largely because universal use of prophylactic antibiotics is counter to the tenets of antimicrobial stewardship.[308,309] In some studies with long-term surveillance, both SDD and SOD were associated with an increase in resistance to ceftazidime in Gram-negative flora of the respiratory tract, although systemic antibiotics were also given in many cases.[310–312] In the short term, however, a systematic review found a significant reduction in resistance of Gram-negative bacilli to third-generation cephalosporins during the use of selective decontamination.[208] The relevance of findings from one country to another is unclear when patterns and prevalence rates of resistant Gram-negative bacteria vary so widely. Preparation requires suitable manufacturing units, and administration can be labour intensive.

Recent high-quality studies have provided evidence that daily bathing using chlorhexidine gluconate in ICUs helps to reduce bacteraemia, but there is limited evidence of its specific effect on MDR Gram-negative bacterial infection.[313–316] This has formed part of successful bundles of interventions, but has not been tested as an isolated measure.[236,296,317–319] Some studies that have evaluated chlorhexidine as a single intervention including randomization have failed to demonstrate a reduction in Gram-negative bacteraemia.[314,316,320] There is no strong evidence that daily bathing with chlorhexidine reduces Gram-negative infection or colonization, and there is a risk of development of resistance.[114] The routine use of oropharyngeal chlorhexidine has been associated with an increase in mortality in one systematic review.[321]

Selective decontamination can temporarily suppress excretion of carbapenem-resistant organisms from the gastrointestinal tract and possibly supplement SICPs.[207] In a retrospective analysis of a German outbreak, SDD with colistin and gentamicin as oral solution and gel was used in 14 patients with proven carriage of carbapenemase-producing *K. pneumoniae* KPC-s-KP ST258.[311] Loss of carriage, as defined by three PCR screens 48 h apart, was found at a mean of 21 days in six treated patients (43%), but also in 30% of controls. Resistance to colistin and gentamicin in post-treatment isolates of *K. pneumoniae* rose 19% and 45%, respectively, compared with controls. In a randomized placebo-controlled trial of a regimen based on colistin and neomycin plus treatment of bacteriuria with nitrofurantoin, the detection of ESBL Enterobacteriaceae in rectal swabs was not affected significantly.[322] A randomized trial against placebo used oral gentamicin and topical oropharyngeal gentamicin and colistin for one week, and was directed against carbapenem-resistant *K. pneumoniae* carriage. It produced a significant reduction in carriage at two weeks but not at six weeks.[207] Mortality was not affected significantly, but throat carriage was reduced from 30% to zero in the intervention vs 35% to 30% with placebo ($P < 0.0001$). Isolates did not develop resistance. A lower-quality controlled study reported reductions in faecal and pharyngeal carriage of *Acinetobacter* spp. during colistin-/tobramycin-selective decontamination.[323] Against this, colistin/neomycin/nalidixic acid did not reduce infections or mortality due to MDR Enterobacteriaceae compared with no prophylaxis, but carriage was reduced ($N = 86$, RR 0.28, 95% CI 0.03–2.28).[324]

Evidence

The use of SDD or SOD is associated with a reduction in the incidence of pneumonia due to Gram-negative bacteria. 1+

The use of SDD or SOD is associated with a reduction in the mortality rate. 1+

SOD can be used to reduce excretion of MDR Gram-negative bacteria during an outbreak, but no effect on transmission of infection has been demonstrated, and application can be logistically difficult. 3

Recommendation

The routine use of SDD or SOD is not recommended for control of MDR Gram-negative bacteria. Conditional

9.5. What are the minimum standards to stop spread in public areas, primary care or care homes?

Care homes are recognized as potential reservoirs of MDR pathogens, which can spread among residents, generally as colonizers, and can be re-introduced into hospitals.[325] Publicity may alarm residents, their relatives and carers. Clear information on the standards of infection prevention and control should be available to promote confidence in the quality of care provided. Despite the relatively poor evidence base, guidelines are available for managers and carers.[239,326] In England, the Code of Practice[326] defines what is required to ensure compliance with Care Quality Commission registration requirements for cleanliness and infection control. Following general principles, owners are encouraged to contact the local health protection team in the event of outbreaks of infection, increase cleaning and hand hygiene compliance by patients and staff, conduct root cause analyses, and train staff in infection prevention and control. The prevalence of ESBL Enterobacteriaceae in the care home is usually unknown and sporadic. The need for a urinary catheter, if present, should be reviewed regularly and it should be removed as soon as it is not needed. The appropriate use of such devices to prevent healthcare-acquired infection has been reviewed elsewhere.[166] Residents with diarrhoea should be isolated in their room with a dedicated commode if no ensuite facilities are available. This isolation may require additional psychological support for the resident. Colonization with MDR organisms should not be construed as a reason to isolate or screen other residents. SICPs must continue to be applied.

Evidence

Institutionalized patients/residents are more likely to carry MDR organisms and present a risk on re-admission to hospital. 2+

Good Practice Recommendations

Care homes should adopt national recommendations for environmental and equipment cleanliness, and infection prevention and control.

Clear patient information on MDR Gram-negative infection must be provided in accessible formats to encourage good hand hygiene by patients and staff.

9.6. Are there organizational structures within a healthcare facility that play a role in the successful control of multi-drug-resistant Gram-negative bacilli?

In Israel, with prevalent ST258/KPC *K. pneumoniae*, a self-contained nursing unit with dedicated staff for patients carrying carbapenem-producing Enterobacteriaceae was effective as part of a package of measures including mandatory reporting and a centralized national monitoring system.[77] In the same way, a centralized national system was effective in the control of MRSA in the UK. Outbreaks of carbapenemase-producing *K. pneumoniae* appear to have been controlled by a package of measures, including nursing infected patients in separate units with different staff until discharge or cohorting.[197,262,327–329] The nursing units could be single

rooms, cohorts or wards, but the nurse did not cross between units during the shift. A sequential intervention study found that control was effective when patients were nursed in separate locations with dedicated nursing personnel. The shared medical staff had contact precautions vetted by the dedicated nurse before entering the area.[328] However, the intervention also included education, training, cleaning and screening.

Evidence

A separate unit with dedicated nursing staff rather than part of a ward with shared staff is effective in control packages. 3

Recommendation

Monitor hand hygiene of all staff when patient cohorting is being applied. Strong

10. Further research

- PCR-based tests for swift detection of MDR Gram-negative pathogens require further testing and development to allow cost-effective and rapid screening and detection of carriers.
- Consideration should be given to further investigation of screening patients of long-term care facilities as a means of tracking movement and defining reservoirs of organisms. Longitudinal assessment of patients carrying ESBL-producing organisms, particularly *E. coli* ST131, should be made on admission and discharge to hospitals and nursing homes to detect infection and spontaneous clearance of carriage.
- The risk factors for development of infection, such as urinary catheterization, should be separated from the risk factors for carriage, including hospitalization. Household contacts of cases of infection with *E. coli* ST131 or carbapenem-resistant *K. pneumoniae* should be examined for evidence of spread or subsequent infection.
- Given the recent changes in the prevalence of, for example, ESBL-producing *E. coli* ST131 and *K. pneumoniae* ST258 with KPC carbapenemases, the potential for screening patients for particular clones as means of controlling transmission in hospitals should be assessed. MALDI-ToF, serological and DNA-based detection methods should be developed, together with selective or indicator media for quinolone-resistant Enterobacteriaceae.
- Bacteraemia surveillance including sequence typing for strains resistant to cephalosporins, fluoroquinolones and carbapenems should be expanded and open to public and commissioning groups. This is essential for accurate risk assessment of patients transferred between healthcare facilities. In localities with outbreaks, typing and infection control should be extended to isolates from other anatomical sites.
- Randomized intervention studies of effectiveness measures, including single-room isolation, in the prevention of transmission of Gram-negative bacterial infection.
- The potential for endoscopes to disseminate MDR Gram-negative pathogens requires better understanding with reference to complex instruments such as those with wire-containing channels.

Conflict of interest statement

See full details in Section 4.4.

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Appendix 1. Glossary

Active surveillance: Admission regimen that involves testing of patients to detect the presence of multi-drug-resistant organisms.

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

Antimicrobial: A substance that kills or inhibits the growth of micro-organisms.

Augmented care area: Units where medical/nursing procedures render the patients susceptible to invasive disease from environmental and opportunistic pathogens (e.g. critical care, neonatal, burns and haematological wards).

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

safety, including exposure to infections (e.g. disposable gloves and disposable aprons).

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

Screening of patients: Sampling potential colonization sites for multi-drug-resistant Gram-negative pathogens.

Selective decontamination: The prophylactic use of topical and systemic antibiotics to remove pathogenic organisms from the gastrointestinal tract to reduce the incidence of respiratory tract infections.

Standard infection control precautions (SICPs): Basic infection prevention and control measures necessary to reduce the risk of transmission of infectious agents from both recognized and unrecognized sources of infection. Sources of (potential) infection include blood and other body fluid secretions or excretions (excluding sweat), non-intact skin or mucous membranes, and any equipment or items in the care environment that could have become contaminated.

Appendix 2. Guideline development

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

Conflict of interest

Conflicts of interest were registered at the outset and renewed during the process. They are stated in the report. In the event of a potential conflict being identified, the Working Party agreed that the member should not contribute to the section affected.

Infection control: systematic review process

Patient Intervention Comparison Outcome process

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

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

Comparisons: Comparisons between intervention and standard management were used.

Outcomes: Objective referring to length of hospital stay, mortality, rate of acquisition or infection.

Systematic review questions

1. What is the definition of MDR Gram-negative bacilli?

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

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

Care area: Any portion of a healthcare facility where patients are intended to be examined or treated.

Cleaning: Methods that physically remove soil, dust and dirt from surfaces or equipment.

Cohorting: Imposed grouping within an area of a hospital ward of patients or staff potentially exposed to designated diseases.

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

Community-acquired: Infection or colonization that is acquired outside of hospitals.

Community-associated: Usually defined as infection or colonization detected in an outpatient or within 48 h of hospital admission.

Contact precautions: Hand hygiene is performed before touching the patient and prior to wearing gloves, and wearing gloves when touching the patient and the patient's environment. A single room is preferred; otherwise, discussion with infection control personnel to consider cohorting or not moving the patient. An apron/gown is worn for all patient interactions that may involve contact with the patient or potentially contaminated areas in the patient's environment. Donning personal protective equipment on room entry and discarding before exiting the patient room is required to contain pathogens, especially those that have been implicated in transmission through environmental contamination.[173]

Extended-spectrum β-lactamases (ESBLs): β-lactamases that attack cephalosporins with an oxyimino side chain (e.g. cefotaxime, ceftriaxone and ceftazidime), as well as the oxyimino-monobactam aztreonam. Unlike AmpC β-lactamases (q.v.), they are inhibited by clavulanic acid and tazobactam, and unlike carbapenemases (q.v.), they do not attack carbapenems

Healthcare-associated (acquired): Infection or colonization detected in an inpatient more than 48 h after hospital admission.

High-risk: Used to describe those patients or facilities where the risk of acquiring infection is in the upper 10% of the total patient population.

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

Long-term care facility (care home/nursing home): Provides accommodation and meets the needs of patients with chronic illness or disability who cannot care for themselves.

Multi-drug-resistant (MDR) Gram-negative bacteria: Bacteria resistant to at least three different antibiotics.

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

Passive surveillance: Review of routine clinical samples of all patients by microbiologists on reporting results from the laboratory.

Personal protective equipment: The equipment a person wears to protect themselves from risks to their health or

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

Antimicrobial chemotherapy: systematic review process

Systematic review questions

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

Databases and search terms used 23rd May 2014[358]

Databases

The Cochrane Library; MEDLINE; EMBASE; CINAHL

MeSH terms Appendix F, see online supplementary materiial

Search dates: Medline 1946–2014; Embase 1980–2012; CINAHL (1984–2012)

Search results (Figure 1)

Total number of articles located after duplicates removed = 2523

Sift 1 criteria

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

Articles retrieved

Total number of studies selected = 597

Sift 2 criteria

Full text confirms that the article is primary research (randomized controlled trial, non-randomized controlled trial, controlled before–after study, interrupted time series, case–control study, case series, prospective cohort, systematic review), informs one or more review questions

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

Total number of studies selected = 49

Critical appraisal

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

Accepted and rejected evidence

No meta-analyses were available

Accepted after critical appraisal = 49

Rejected after critical appraisal = 0

Appendix 3. Consultation stakeholders

Antimicrobial Resistance and Hospital Acquired Infection Advisory Committee

British Medical Association

British Society of Antimicrobial Chemotherapy

British Infection Association

C. Diff Support

European Society of Clinical Microbiology and Infectious Diseases

Faculty of Intensive Care Medicine
Foundation Trust Network
Hand Hygiene Alliance
Healthcare Infection Society
Infection Prevention Society
Lee Spark Foundation
MRSA Action UK
NHS Confederation
NHS England
NHS Trust Development Authority
Patient's Association
Public Health England/Wales/Scotland/Northern Ireland
Royal College of Pathologists
Royal College of General Practitioners
Royal College of Nursing
Royal College of Physicians
Royal College of Surgeons
Service User Research Forum Healthcare Acquired Infections
UK Clinical Pharmacists Association
Unison

Appendix 4. Continuing Professional Development material

1. In deciding which patients to screen for carbapenem-resistant organisms, which two groups should take priority:

a) Admitted to intensive care
b) Admitted to surgical ward
c) Admitted from long-term care facility
d) Admitted to medical ward
e) Discharge to community

Answer: A C

2. For the purposes of national surveillance, which two antimicrobial susceptibilities for Gram-negative pathogens are most important to test?

a. Meropenem
b. Amoxicillin
c. Trimethoprim
d. Gentamicin

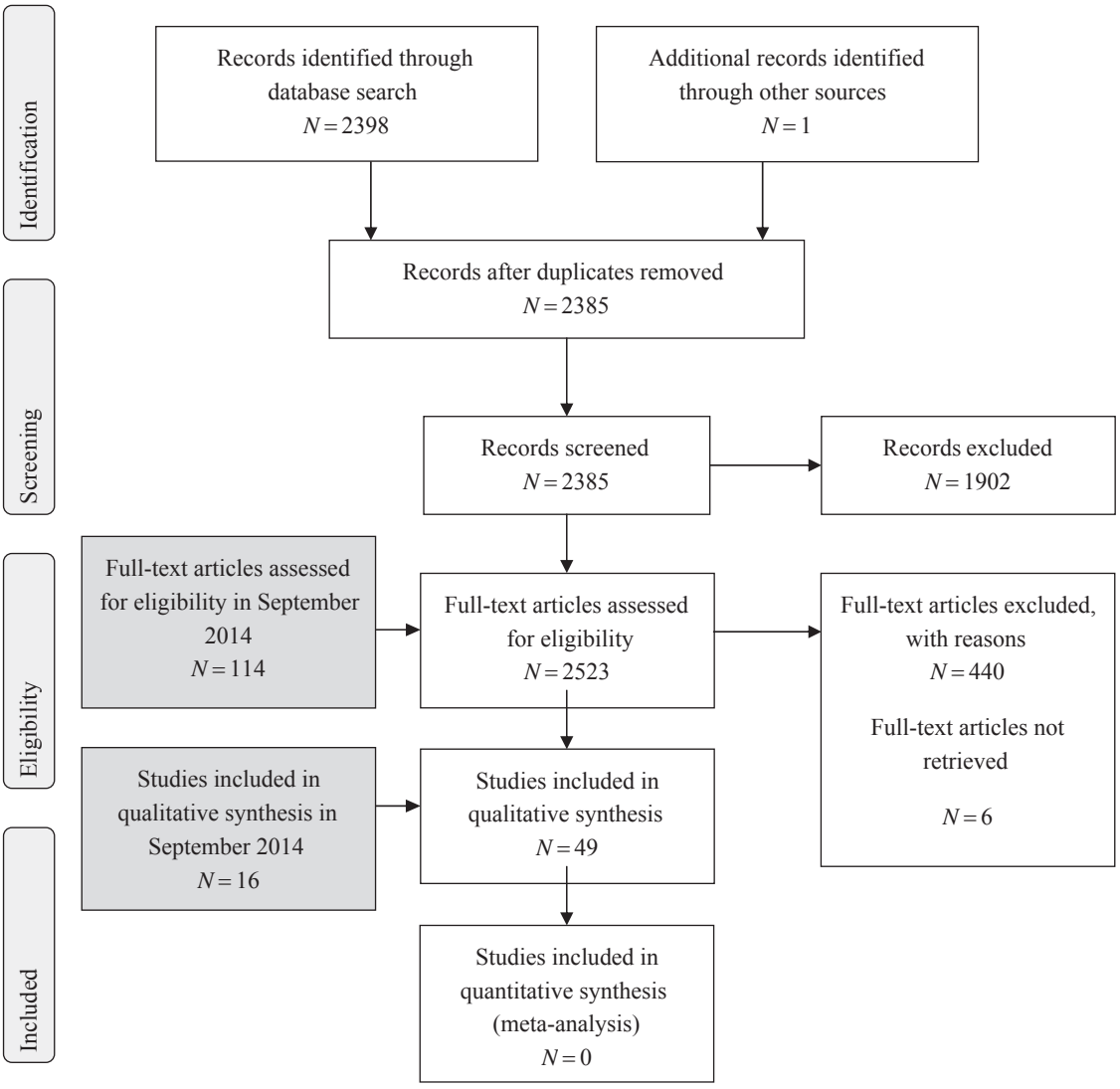

Figure 1. Flow chart of systematic review.

e. Cefpodoxime
Answer: A E

3. To prevent spread of multi-drug-resistant Gram-negative pathogens:
a. Assess all patients for risk of infection on arrival
b. Maintain standard infection control precautions in only those patients at high risk
c. Do not discard body fluids into hand basins
d. Minimize use of invasive medical devices
e. Audit and feedback staff compliance
Answer: A C D E

Appendices A—G. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.jhin.2015.08.007.