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ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients

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Abstract

Healthcare-associated infections due to multidrug-resistant Gram-negative bacteria (MDR-GNB) are a leading cause of morbidity and mortality worldwide. These evidence-based guidelines have been produced after a systematic review of published studies on infection prevention and control interventions aimed at reducing the transmission of MDR-GNB. The recommendations are stratified by type of infection prevention and control intervention and species of MDR-GNB and are presented in the form of 'basic' practices, recommended for all acute care facilities, and 'additional special approaches' to be considered when there is still clinical and/or epidemiological and/or molecular evidence of ongoing transmission, despite the application of the basic measures. The level of evidence for and strength of each recommendation, were defined according to the GRADE approach.

Keywords: *Acinetobacter*, *Burkholderia*, Enterobacteriaceae, extended-spectrum *β*-lactamase, guideline, infection control, multidrug-resistant Gram-negative, outbreak, *Pseudomonas*, *Stenotrophomonas*

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These guidelines are endorsed by Società Italiana Malattie Infettive e Tropicali (SIMIT), Brazilian Association of Professionals in Infection Control and Hospital Epidemiology (ABIH), Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC), Società Italiana Multidisciplinare per la Prevenzione delle Infezioni nelle Organizzazioni Sanitarie Italiana Malattie (SIMPIOS), Indian Association of Medical Microbiologists Delhi & NCR Chapter (IAMM DC and NCR), and Colombian Association of Hospital Epidemiology (ACEH).

Introduction

Healthcare-associated infections (HAIs) are a leading cause of morbidity and mortality worldwide. Therapy is becoming ever more difficult because of the increasing rate of antimicrobial resistance among common HAI pathogens. Over the last decade, multidrug-resistant Gram-negative bacteria (MDR-GNB), including MDR-*Pseudomonas aeruginosa*, MDR-*Acinetobacter baumannii* and Enterobacteriaceae producing extended-spectrum β-lactamases (ESBL) and carbapenemases, have been implicated in severe HAIs and their occurrence has increased steadily.

In 2011, the European Antimicrobial Resistance Surveillance System network (EARS-Net), including 29 European countries, reported a general European-wide increase of antimicrobial resistance in the Gram-negative pathogens under surveillance (*Escherichia coli*, *Klebsiella pneumoniae* and *P. aeruginosa*; available from: http://www.ecdc.europa.eu/en/publications/Publications/Forms/ECDC_DispForm.aspx?ID=998). The proportion of reported *E. coli* isolates resistant to third-generation cephalosporins (most of which were ESBL-producers) ranged from 3% to 36% and had increased significantly over the last 4 years in more than half of EARS-Net reporting countries. High proportions of antimicrobial-resistant *P. aeruginosa* have been reported by many countries, especially in southern and eastern Europe, with 15.3% of isolates resistant to at least three antimicrobial classes and 4.6% resistant to all five antimicrobial classes under surveillance. Trends of carbapenem resistance showed a significant increase between 2008 and 2011 for five countries (Austria, Cyprus, Denmark, Greece and France). In 2011, 22.3% of all *K. pneumoniae* invasive isolates were resistant to at least three antimicrobial classes. Remarkably, a significant increase in resistance to carbapenems in *K. pneumoniae* from 8% to 15% was reported over the period 2005–2010 (available from: http://www.ecdc.europa.eu/en/publications/Publications/Forms/ECDC_DispForm.aspx?ID=580).

In the USA, data reported to the Centers for Disease Control and Prevention (CDC) National Nosocomial Infection Surveillance System and the National Healthcare Safety Network reflect an increase over the past decade in rates of infections caused by some MDR-GNB, defined as resistance to one or more tested antimicrobials in three or more antimicrobial classes [1]. Among Gram-negative organisms associated with central line-associated bloodstream infections, catheter-associated urinary tract infections, ventilator-associated pneumonia and surgical site infections that were reported to the National Healthcare Safety Network during 2009–2010, approximately 15% of *K. pneumoniae* or *Klebsiella oxytoca*, 2% of *E. coli*, and 65% of *A. baumannii* isolates met MDR-GNB criteria. Moreover, nearly one-fifth of hospitals reporting central line-associated bloodstream infections or catheter-associated urinary tract infections due to *Klebsiella* species noted the occurrence of carbapenem-resistant *Klebsiella* isolates, reflecting the penetration of MDR-GNB into the microbiological milieu of many US hospitals [1]. As in many other countries, the emergence of carbapenemase-producing Enterobacteriaceae, and in particular *K. pneumoniae* isolates containing the bla_{kpc} gene, has become a major healthcare epidemiology issue, with the ST258 multilocus sequence type strain accounting for approximately 70% of *K. pneumoniae* carbapenemase-producing isolates sent to the CDC [2]. Of even greater concern is the rapid spread, both in the USA and in Europe, of Enterobacteriaceae harbouring the New Delhi metallo-β-lactamase and the *K. pneumoniae* carbapenemase in hospitalized patients [3].

The infection prevention and control (IPC) measures that have been applied in hospitals for MDR-GNB vary widely, both within and between different countries [4]. A harmonized approach, deriving from the application of evidence-based core strategies and comprising specific strategies that related to local characteristics and context, should result in a more comparable situation. However, there is no consensus as to the most effective IPC interventions or the best combination of interventions to reduce transmission of MDR-GNB in hospitalized patients. In particular, there is no consensus on species or types that are more likely to require control measures, or on the role of screening to identify carriers. Previous guidelines have either not addressed, or have provided only limited consideration to IPC implications of MDR-GNB. The Health Care Infection Control Practices Advisory Committee (HICPAC)/CDC guidelines, published in 2006, provided only generic guidance for control of all MDR-organisms [5]. Guidance documents for control of HAIs due to carbapenem-resistant Enterobacteriaceae (CRE) were published in 2009 [6] and in 2012 by the CDC (available from: http://www.cdc.gov/hai/organisms/cre/cre-toolkit/index.html) and in 2011 by the European Centre for Disease Prevention and Control (ECDC) (available at http://ecdc.europa.eu/en/publications/Publications/110913_Risk_assessment_resistant_CPE.pdf). Although these publications focus on controlling the spread of MDR-GNB strains, they do not provide an analysis of the strength of recommendations or grade of evidence.

We performed a systematic review of the articles published on this topic to determine the effects of different IPC interventions aimed at minimizing the spread of MDR-GNB and to define the indications for application of IPC measures

for specific types of resistant strains in adult hospitalized patients. Our guidelines have been drawn up so as to be useful for a wide range of healthcare professionals, namely specialist physicians and other healthcare workers (infectious diseases, microbiology, surgery, intensive care), public health officers, infection control professionals, administrative personnel in hospitals, and epidemiologists.

Methods

Articles presenting data pertaining to the control of the spread, in hospitalized patients, of MDR-*P. aeruginosa*, *A. baumannii* and Enterobacteriaceae and organisms intrinsically resistant to broad-spectrum antimicrobial agents, such as *Stenotrophomonas maltophilia* and *Burkholderia cepacia*, were identified through computerized literature searches using MEDLINE (National Library of Medicine Bethesda, MD), EMBASE and the Cochrane database and by reviewing the references of retrieved articles. For the development of the background section we also reviewed articles describing the epidemiology of target bacteria. MDR organisms were defined according to the ECDC/CDC definition [7] as those micro-organisms that were resistant to at least one agent in three or more antimicrobial categories. Index search terms included: '*Pseudomonas*' or '*Citrobacter*' or '*Enterobacter*' or '*Escherichia*' or '*Klebsiella*' or '*Morganella*' or '*Proteus*' or '*Providencia*' or '*Serratia*' or '*Acinetobacter*' or 'Enterobacteriaceae' or '*Stenotrophomonas maltophilia*' or '*Burkholderia cepacia*' and 'drug resistance' or 'antibiotic resistance' and 'cross infection' or 'infection control' or 'infection prevention' or 'patient isolation' or 'cohorting' or 'gloves' or 'protective clothing' or 'handwashing' or 'hand hygiene' or 'sanitizer' or 'cleanser' or 'disinfectant' or 'pre-emptive isolation' or 'antisepsis' or 'disinfection' or 'sterilization' or 'environmental cleaning' or 'screening culture' or 'disease outbreaks' or 'antibiotic restriction or cycling'. The search was restricted to full articles published in English up to November 2011 and including adult patients (>16 years of age). Articles reporting intervention(s) on paediatric population were excluded. No attempt was made to obtain information on unpublished studies. As data from randomized clinical trials were expected to be limited, we also reviewed non-randomized controlled clinical trials, interrupted time-series, and before-and-after studies that compared wards or hospitals applying two different intervention policies to control the spread of MDR-GNB. We also reviewed outbreak investigations and cohort studies. Single case reports were excluded. Papers were reviewed according to the epidemiological setting (outbreak versus endemic, see Table 1). The term 'outbreak' was defined as an unusual or unexpected increase of cases of infections due to MDR-GNB already isolated in the hospital or the emergence of cases of infection due to a new MDR-GNB, with or without molecular analysis of strains. 'Endemic' was

TABLE 1. Definitions of epidemiological setting

Endemic	Settings where there are constant challenges from admissions of patients colonized or infected with MDR-GNB
Epidemic (outbreak)	Settings where there is an unusual or unexpected increase of cases of infections due to MDR-GNB already isolated in the hospital or an emergence of cases of infection due to a new MDR-GNB, with or without molecular analysis of strains

MDR-GNB, multidrug-resistant Gram-negative bacteria.

TABLE 2. Quality of evidence and strength or recommendations according to the GRADE approach (available from: http://www.gradeworkinggroup.org)

Quality of evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect
Strength of recommendations	
Strong	Large differences between the desirable and undesirable consequences. High confidence in the magnitude of estimates of effect of the interventions on important outcomes
Conditional	Small net benefit and low certainty for that benefit. Great variability in values and preferences, or uncertainty in values and preferences. High cost of an intervention

TABLE 3. Factors increasing or decreasing the level of studies' quality according to the GRADE approach (available from: http://www.gradeworkinggroup.org)

Study design	Initial quality of a body evidence	Decrease quality	Increase quality
Randomized trials	High	Risk of bias	Large effect (RRR 50% or RR 2)
		Inconsistency	Very large effect (RRR 80% or RR 5)
Observational studies	Low	Indirectness	Dose response
		Imprecision	All plausible residual confounding may be working to reduce the demonstrated effect or increase the effect if no effect was observed
		Publication bias	

RRR, relative risk reduction; RR, relative risk.

applied to settings where there were constant challenges from admissions of patients colonized or infected with MDR-GNB, but with no major changes over time recognized as distinct acquisition from a common source. The various types of IPC interventions used to prevent and control the spread of MDR-GNB were grouped into five main categories: hand hygiene measures (HH); active screening cultures (ASC); contact precautions (CP); environmental cleaning (EC); and antimicrobial stewardship (ABS).

The quality of studies was classified as high, moderate, low or very low, whereas the strength of recommendations was classified as strong or conditional according to the GRADE methodology (available from: http://www.gradeworkinggroup.org). Tables 2 and 3 describe in detail the GRADE approach, grades of evidence and determinants of quality. In case of disagreement among members, the quality of the paper reporting outbreaks was further defined through the ORION checklist for outbreak reporting [8]. For the cumulative evidence the authors agreed that an overall 'moderate' classification required at least one intervention of 'moderate' quality and that the sum of 'moderate' research study(ies) plus 'low' research study(ies) needed to be ≥50% of the available evidence. For the development of guidelines, the Standard and Practice Guidelines Committee recommendations were followed (available from: http://www.idsociety.org/Guideline_Resources/).

The major limitation of grading the evidence for IPC measures and MDR-GNB was related to the fact that almost all measures were included in different combinations in multifaceted approaches. When multiple interventions were introduced in different moments the authors analysed the single intervention according to the related magnitude of the effect. In case of multiple interventions introduced at the same moment, the evidence and strength of recommendations were derived from the cumulative evaluation of the efficacy of the whole bundle where the specific IPC measure was included.

Mechanisms of Transmission

A review of the literature on mechanisms of transmission of MDR-GNB was problematic for three main reasons: (i) the low number of studies; (ii) the low availability of high-quality studies; and (iii) the high heterogeneity of definitions, settings and pathogens. Patient-to-patient transmission was frequently thought to be the most important route of transmission whenever several patients shared clonally related isolates. This is based on the hypothesis that colonized or infected patients are the only reservoir for the microorganism. However, intermediate vectors for spread between patients, including contaminated hands of healthcare workers (HCWs), environment, and visitors should also be taken into consideration for the prevention and control of healthcare-associated MDR-GNB transmission.

Extra-intestinal pathogenic *Escherichia coli*

Although an important cause of HAIs, *E. coli* is mainly a community pathogen. As the constant influx of community isolates colonizing patients at hospital admission is highly significant in the epidemiology of these organisms within hospitals, understanding the complex epidemiological behaviour of *E. coli* in the community is key to adequate interpretation of studies addressing the epidemiology of *E. coli* in hospitalized patients. This microorganism belongs to the normal bowel flora in humans, other mammals and birds. Strains have traditionally been classified as commensal (because they less frequently cause disease and mainly belong to phylogenetic group A and B1), intestinal pathogenic (mainly obligate pathogens) and extra-intestinal pathogenic (most often of phylogenetic groups B2 and D). The latter are the predominant strains in 20% of individuals and harbour the typical virulence factors causing extra-intestinal infections when reaching the appropriate site from the bowel, which

serves as their primary reservoir [9]. Transmission of extra-intestinal pathogenic *E. coli* in the community is thought to occur by person-to-person transmission, either through direct contact or by means of a faecal–oral route through or by contaminated food and/or water [10]. Several clonal groups of antibiotic-resistant extra-intestinal pathogenic *E. coli*, specifically, O15:H1-D-ST393, CGA-D-ST69, and O25b:H4-B2-ST131 are extensively distributed and mainly associated with community outbreaks of urinary tract infections [10–15]. It is probable that the spread of these clonal groups within the hospitals had occurred much earlier, but went unnoticed in the absence of an epidemiological marker, such as antibiotic resistance. Food was suspected as the main source for O15:H1-D-ST393 and CGA-D-ST69 [10] but the main sources and mechanisms of transmission for O25b:H4-B2-ST131 are not yet clear.

The epidemiology of *E. coli* within healthcare facilities has not been extensively studied. Researchers have mainly focused on MDR isolates. However, the reservoirs and mechanisms of transmission have rarely been investigated. The results of molecular typing need to be interpreted with caution. The finding of clonally related strains does not necessarily mean that there was transmission within the healthcare institution, but rather may reflect the influx of a successful clone or clones from the community [16–19]. Community isolates belonging to such clonal groups have shown a high degree of similarity in pulsed field gel electrophoresis dendrograms, even when isolated from patients from different areas [15]. Hence, findings from molecular typing of nosocomial isolates must be combined with knowledge of community-circulating clones and the clinical epidemiology (e.g. date of admission and when the first screen was positive) for meaningful interpretation. Such data may, of course, also provide evidence of a constant influx of clonally diverse strains from the community. Without such detailed epidemiological information, one might otherwise mistakenly consider such a situation to comprise a nosocomial outbreak. Finally, contaminated food products are known to be frequent vehicles for *E. coli* strains [20]. However, the significance of alimentary transmission of antibiotic-resistant *E. coli* within hospitals has been poorly studied in developed countries.

In the 1960s and 1980s some nosocomial outbreaks of pyelonephritis were indirectly associated with transmission from HCWs [21–23]. In 2001, Paterson *et al.* [24] reported a clonal outbreak caused by ESBL-producing *E. coli* in a liver transplantation unit causing bacteraemia in two patients, with seven others only colonized. The epidemic strain was not found either in the environment or on the hands of staff. CP and intestinal decolonization of patients with norfloxacin, active against the outbreak strain, was instituted and the outbreak was eradicated.

A few studies have tried to identify environmental reservoirs, despite the fact that in some instances patients harbouring the clonally related isolates did not have overlapping stays in the unit. In a study performed in Brazil, *E. coli* was found on the hands of only one out of 100 HCWs, whereas other organisms were found much more frequently [25]. In a study on Intensive Care Unit (ICU) patients, Harris *et al.* [26] found 23 patients out of a total of more than 1800 admissions to have acquired colonization with ESBL-producing *E. coli* during their ICU stay. In only three of these 23 patients the isolates were identical by pulsed field gel electrophoresis to those found in 74 other patients colonized upon admission screening, suggesting that patient-to-patient transmission was not an important cause of acquisition of ESBL-producing *E. coli* in this ICU in a non-outbreak setting. Once again, environmental or food sources were not investigated.

Recently, three studies have investigated the transmission dynamics of ESBL-producing *E. coli*. Adler *et al.* [27] focused their study in two geriatric rehabilitation wards in Israel. They found that 32 out of the 59 'new acquisitions' (54%) were traced to another patient and this was particularly frequent for two specific clones (ST131 producing CTX-M-27 and ST372 producing SHV-5). Interestingly, the situation differed in a Swiss tertiary hospital, where ESBL-producing *E. coli* was acquired only by 1.5% of hospital patients in contact with colonized/infected patients [28]. In addition, in another study the transmission of ESBL-producing *E. coli* was shown to be more frequent in households than in the hospital setting [29]. These results suggest that person-to-person transmissions of some ESBL-producing *E. coli* occur, but are not common in most hospital settings.

Klebsiella species

There have been several recent studies of the epidemiology of *K. pneumoniae* as a nosocomial pathogen. This organism shows a clear trend to spread clonally within healthcare institutions and exhibits a particular ability to cause nosocomial outbreaks [30,31]. This may be a feature of some specific successful clones and antibiotic resistance may provide an additional advantage in healthcare settings to such clones. Cross-transmission via HCWs' hands seems to be important in the nosocomial spread of *K. pneumoniae* strains [31]. Indeed there is extensive evidence for transmission via the hands of HCWs from colonized patients or environmental reservoirs to new patients, in both epidemic and endemic situations [32–47]. However, in a recent study, an outbreak caused by contaminated food was described, indicating that transmission may also occur via the food chain [48]. Additionally, transmission from contaminated sinks has been recently shown for ESBL-producing *K. oxytoca* [49].

Other Enterobacteriaceae

Enterobacter spp. and *Serratia* spp. (particularly *Enterobacter cloacae* and *Serratia marcescens*) are important nosocomial pathogens and outbreaks caused by these organisms have been documented. Cross-transmission via transient contamination of HCWs' hands has also been well documented in epidemic and endemic situations [50–65] and outbreaks of bacteraemia involving both species have also been linked to contaminated medical products [51]. Contamination both of dry surfaces and moist environments was particularly frequent when looked for, suggesting that environmental contamination played a central role in many outbreaks.

Nosocomial outbreaks caused by *Salmonella* spp. have also been described. Although most of these were probably food-borne-related, cross-transmission through the hands of HCWs was also suspected to have occurred [66–69].

Non-fermentative GNB

Pseudomonas aeruginosa is commonly associated with moist environmental sources. Colonized patients may serve as reservoirs for epidemic strains. However, the epidemiology of this organism is complex, as sporadic and epidemic strains usually coexist, so that outbreaks may be difficult or impossible to trace unless molecular methods are used [70,71]. The source and mechanism of transmission of different strains may vary. HCWs' hands can be contaminated from patient or environmental sources [25,41,71–75]. Hence, patients may acquire the organism from the environment, e.g. when using contaminated sinks, showers or respiratory equipment, or via HCWs' hands. Patient-to-patient transmission of epidemic clones of *P. aeruginosa* among patients with cystic fibrosis has been documented. Recent experimental and clinical data showed that patients with cystic fibrosis can generate droplet nuclei in the respirable range and that infectious particles can be cultured from room air minutes to hours after patients have left [76]. Data from the USA showed that the rate of bacterial contamination of cystic fibrosis clinics with respiratory tract pathogens, including *P. aeruginosa*, was 13.6%; the air collected within 3 feet (90 cm) of patients, their hands, and the environment was contaminated during 8.2%, 6.2% and 1% of visits, respectively [77,78].

The epidemiology of *A. baumannii* has been thoroughly reviewed [79]. *Acinetobacter baumannii* may cause monoclonal outbreaks, usually related to an environmental source, or as complex, extensively polyclonal situations, in which epidemic and sporadic clones coexist [80,81]. Environmental contamination, both of dry and moist areas, is key to the dissemination of *A. baumannii*. Colonized patients may serve as effective reservoirs and HCWs' hands can serve as vehicles for transmission either from contaminated surfaces to patients or between patients.

Nosocomial infections caused by *Stenotrophomonas maltophilia* are usually caused by sporadic strains, probably acquired from different environmental wet sources [51]. However, a few outbreaks of indistinguishable strains related to a common environmental source or cross-transmission have been reported [82–85]. *Burkholderia cepacia* may also cause nosocomial outbreaks, typically associated with medical products or environmental moist sources [51,82] Cross-transmission has been documented between cystic fibrosis patients [86,87] and may occur among non-cystic fibrosis patients [88].

The Role of Hand Hygiene to Prevent Spread of MDR-GNB

The role of HCWs' hand contamination has been under investigation since the 1960s [89]. Before performing hand disinfection, up to 40% of nurses' hands yielded coliform bacteria, although rates depended on the type of unit sampled [33,90]. Another study showed that 17% of ICU staff carried *Klebsiella* spp. on their hands and that these strains were probably related to colonized or infected patients resident in the unit [91]. An epidemic MDR-*Klebsiella* spp. survived on fingertips better than susceptible strains and persisted longer than *E. coli* and *P. aeruginosa* [91]. Coliforms can be picked up on the hands of nurses after touching patients' washing materials and clothing, as well as after bed-making, toileting activities, handling bed linen and curtains, and even after administering medications to the patients [92]. Transfer of viable amounts of *Klebsiella* spp. to nurses' hands took place after simple 'clean' procedures, such as washing the patient and touching several parts of the body during nursing activities (i.e. taking blood pressure, pulse and oral temperature) [33]. Sampling patients' hands on a specific ward demonstrated rates of coliform carriage similar to rates of carriage for nurses on that ward [92]. Hand contamination despite wearing gloves has been reported in 4.5% and 1% of HCWs after caring for MDR-*A. baumannii* and MDR-*P. aeruginosa* colonized or infected patients, respectively [93].

The mechanism of microbe cross-transmission is summarized in the World Health Organization (WHO) 2009 HH guidelines 'five moments' (available from: http://whqlibdoc.who.int/publications/2009/9789241597906_eng.pdf): (1) presence of microbes on patient skin and/or in patient's environment, (2) transfer of these organisms to HCWs' hands, (3) microbe survival on HCWs' hands, (4) incorrect hand cleansing by HCWs, and (5) cross-transmission to other patients. The following section will focus on the different 'moments' of cross-transmission of GNB according to the five-step-WHO sequence.

(1) *Microbes on patient's skin and environment*. The number of GNB on the skin is strikingly low if compared to the high level of GNB colonizing the gut. GNB counts in the intestine reach 10^9–10^{11} CFU/g of homogenized tissue, while they are virtually absent from large areas of skin [94]. GNB are isolated more frequently from axilla, perineum and toe webs, which represent humid and partially occluded areas, where the skin bacterial count is highest (10^6–10^7 CFU/cm^2) [94,95]. Recent molecular data show that GNB can be found in abundance on some dry skin sites, including parts of the hands [94].

Acinetobacter calcoaceticus is the GNB most frequently found on normal skin, colonizing up to 25% of individuals [96]; other GNB are identified less commonly as part of the transient skin flora. Hospitalized patients, unlike healthy subjects, may have higher rates of skin colonization with *Acinetobacter* species and other GNB, especially in the perineal area [97–100].

(2) *Transfer of GNB to HCWs' hands*. Many studies over the last decades have reported that up to 100% of HCWs' hands can be contaminated by GNB, including Enterobacteriaceae, *P. aeruginosa*, *Acinetobacter* spp. and other potential pathogens [33,101,102]. GNB counts on HCWs' hands may vary substantially and are related to the type of contact with the patient or the patient's immediate environment. The risk of hand contamination has also varied depending on the microbe. Morgan *et al.* evaluated about 200 opportunities of staff providing assistance to patients colonized or infected with MDR-*A. baumannii* and MDR-*P. aeruginos*a. They observed hand contamination in 4.5% of HCWs assisting patients with MDR-*A. baumannii*, compared with 0.7% of those caring for patients with MDR-*P. aeruginosa*. Risk factors for HCWs' hand contamination with MDR-*A. baumannii* were manipulation of wound dressings, staying in the patients' rooms for more than 5 min, and being a physician or nurse practitioner [93]. Rodriguez-Baño *et al.* [81] observed rates of HCWs' hand colonization by MDR-*A. baumannii* between 12% and 20% in an ICU where this organism was endemic.

A team from the University of Maryland investigated the frequency of transfer of pathogens during the treatment of ICU patients with MDR-*A. baumannii* and/or MDR-*P. aeruginosa* [103]. Contamination of HCWs' gloves and hands verified after glove removal but before hand hygiene was observed in 29.3% and 4.2% of HCWs with MDR-*A. baumannii*, respectively, and in 17.4% and 3.5% with MDR-*P. aeruginosa*, respectively [103].

(3) *Microbe survival on HCWs' hands*. GNB may survive on HCWs' hands for periods lasting from a few minutes to several hours, depending on the species. Notably, GNB have been isolated from the hands of individuals not involved in healthcare in proportions similar to those reported for HCWs [101]. *Acinetobacter* spp. may be isolated from skin for long periods of time after inoculation [104], usually longer than other GNB. Fagernes and Lingas demonstrated that wearing jewellery, such as a single ring, may triple the risk of Enterobacteriaceae hand carriage [105]. Sampling was performed while HCWs were on duty and no evaluation of post-duty hand colonization was performed. Artificial fingernails became colonized with GNB more frequently than natural nails and alcohol-based hand rubs were less effective in eliminating GNB from the former than the latter [106]. Artificial fingernails have been associated with HAIs, including outbreaks of bloodstream infections due to *Serratia marcescens* in haemodialysis patients [107] and of ESBL-producing *K. pneumoniae* and *P. aeruginosa* invasive infections in neonatal ICUs, although the associations were weak [108].

(4) *Incorrect hand cleansing by HCWs*. In one study, if no or inadequate HH was performed during patient care, the level of hand contamination increased progressively in a linear fashion over time, so favouring cross-transmission [102]. A significant reduction in microbe counts has been reported by a limited number of studies evaluating hand washing and/or hand rubbing, although data regarding MDR-GNB are scarce. Paul *et al.* observed a significant reduction in GNB counts when HH was performed both with soap and water and with alcohol hand-rubs soap [109]. Data show that alcohol-based hand-rubs could reduce *A. baumannii* counts by 98% from experimentally contaminated hands [110].

(5) *Cross-transmission to other patients*. The prevalence of possible cross-transmission of GNB among patients is difficult to evaluate. Studies in the ICU population applying conventional and molecular methods report percentages of cross-transmission ranging from 23% to 53% of patients' contacts [111,112]. Lingaas and Fagemes [113] developed a method to investigate the transfer of *E. coli* from the hands of HCWs. The method involved standardized hand contact between the HCW and a recipient wearing sterile gloves, followed by sampling of the bare hands of the HCW and the gloved hands of the recipient by the glove juice method. A smaller proportion of *E. coli* was recovered from bare skin compared with gloves, suggesting reduced survival of bacteria as a result of contact with natural skin [113].

Clothing of HCWs can be contaminated by nosocomial pathogens and therefore be a source for cross-transmission of healthcare-associated pathogens [114–119]. Such attire is

progressively contaminated by an HCWs' own flora, which is generally of low pathogenicity and constitutes about a third of the isolated germs. Flora from patients or the hospital environment represents the remaining two-thirds of microorganisms found on clothing [116,119]. The areas of attire with the heaviest colonization are the zones most frequently touched by hands, i.e. below the waist, and on the sleeves and pockets [114,115,119]. In one paper, the level of bacterial contamination did not vary with the length of time a coat had been in use, but it increased with the degree of usage by the individual doctor [115]. Performing procedures involving heavily contaminated body sites, such as dressing wounds, may cause high levels of clothing contamination [119]. Protective clothing, particularly plastic aprons, have been associated with a significant reduction in clothing contamination in high-risk settings such as burn units [116,120]. During clinical activity other items worn, such as badges and lanyards, may also become contaminated [121].

Contamination of gowns and gloves has been shown to be a frequent event during patient care [93,103]. In particular, gown contamination with MDR-*A. baumannii* has been observed in 11–12% of HCWs when caring for colonized patients [93,103]. In the same studies, MDR-*P. aeruginosa* contaminated HCWs gowns less frequently, i.e. 4–5% [93,103]. Since not all healthcare systems supply uniforms processed in an industrial laundry, staff may need to launder their uniforms at home. Wilson *et al.* [116] show that there is no substantial difference between home and industrial laundering concerning microbial residual contamination.

Recommendations

Epidemic setting

Strong recommendation: Implement HH education programmes to reduce the transmission of ESBL-producing Enterobacteriaceae. MDR-*A. baumannii*, *Stenotrophomonas maltophilia* (moderate level of evidence); MDR-*K. pneumoniae*, MDR-*P. aeruginosa* and *Burkholderia cepacia* (very low level of evidence)

Endemic setting

Strong recommendation: Implement hand hygiene (HH) education programmes to reduce the transmission of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, multidrug-resistant (MDR)-*Klebsiella pneumoniae*, MDR-*Pseudomonas aeruginosa*, MDR-*Acinetobacter baumannii* (moderate level of evidence); *Stenotrophomonas maltophilia* and *Burkholderia cepacia* (very low level of evidence)

The Role of Contact Precautions to Prevent Spread

Basic infection control precautions (i.e. standard precautions) need to be used, as a minimum, in the care of all patients and are meant to reduce the risk of transmission of blood-borne and other microorganisms from both recognized and unrecognized sources. They include HH, and personal protective equipment guided by risk assessment and the extent of contact anticipated with blood and body fluids, or pathogens. In addition to standard precautions, CP include: wearing a gown and gloves upon entry to a room of a patient/resident colonized or infected with epidemiologically targeted bacteria and using disposable single-use or patient/resident-dedicated non-critical care equipment (such as blood pressure cuffs and stethoscopes).

Once MDR-bacteria infection or carriage is detected in hospitalized patients, most international guidelines recommend the application of CP to these patients to prevent hospital spread [5,6]. There are multiple ways of implementing such CP. For example, patients can be transferred to special isolation wards or housed in nursing cohorts, i.e. in separate rooms on general wards with designated nursing staff exclusively responsible for the cohort. Alternatively, colonized patients can be isolated in single or cohort rooms on general wards without designated personnel. Third, the application of CP can be performed housing the patients in the same room with patients unaffected by MDR-GNB, but applying CP (e.g. as defined above including the use of gloves and gowns or aprons depending on the extent of carriage by the patient and the procedures being performed by staff) when caring for the colonized or infected patient. Notably, in the ECDC systematic review to define the effectiveness of IPC measures to decrease the incidence of colonization or infection with CRE, the most effective approach included CP, screening for early detection of CRE-colonized patients, and cohort nursing care for CRE-colonized patients (available from: http://ecdc.europa.eu/en/publications/Publications/110913_Risk_assessment_resistant_CPE.pdf). Suboptimal adherence to CP was linked to limited impact on HAI outcomes.

The efficacy of CP can be optimized through an effective and consistent approach to screening cultures, not only to identify all carriers but also to monitor the success of any isolation or infection prevention measure. An alert code for previously known positive patients followed by pre-emptive CP could help in reducing the spread of MDR-GNB. Evidence derives from successful interventions in the endemic setting on MDR-*P. aeruginosa* [122] and during outbreaks by ESBL-producing Enterobacteriaceae and MDR-*K. pneumoniae* [123–127]. Weekly screening cultures in addition to those on admission and

discharge might optimize the CP, especially in high-risk settings and in case of long hospitalization [125,128,129].

No consensus exists on when CP may be discontinued. The majority of the studies on CP applied this measure until two or three negative screening cultures taken a week apart were obtained. Rarely CP were maintained during the entire hospitalization period.

The authors of these guidelines suggest discontinuing them when three or more screening cultures for the target MDR-organism are repeatedly negative over the course of a week or two in a patient who has not received antimicrobial therapy for several weeks.

There is no study focused on the use of surgical masks as a component of CP in the management of patients with respiratory colonization or infection due to MDR-GNB. A few papers reporting outbreaks due to MDR-*A. baumannii* added masks on top of CP in the ICU settings with favourable results [129–131].

CP in epidemic settings

Effectiveness of CP in controlling an outbreak due to MDR-*A. baumannii* has been reported by Gbaguidi-Haor *et al.* [132] The authors applied CP and patient cohorting for all patients colonized or infected with *A. baumannii*, whatever the antibiotic susceptibility of the strain. Once new cases of colonization or infection due to MDR-*A. baumannii* were no longer detected, the systematic implementation of isolation precautions and patient cohorting was stopped for a 2-year period. A resurgence in the number of *A. baumannii*-colonized or -infected patients led to reimplementation of CP, resulting in a consequent decrease in the incidence of patients with *A. baumannii* colonization or infection. The changes in the application of CP were also associated with a decrease in the number of patients with *A. baumannii* bacteraemia [132].

Ineffectiveness of the implementation of CP and ASC in epidemic setting has been reported. An outbreak of MDR-*A. baumannii* was not controlled by setting up a programme of screening for all patients in addition to immediate isolation or cohorting of colonized patients. Ward closures were necessary to contain the spread of MDR-*A. baumannii* [133]. A possible explanation was that the lack of pre-emptive isolation allowed cross-transmission among patients. Environmental contamination and lack of proper cleaning and disposal of contaminated equipment might have also played a pivotal role in outbreaks [134,135].

The implementation of cohorting of patients and/or staff can improve the effectiveness of a bundle approach to control an outbreak due to MDR-GNB. Laurent *et al.* described the failure of CP, isolation room and ASC in controlling an outbreak of ESBL-producing *K. pneumoniae*. When the infection control measures were reinforced with the introduction of cohorting of colonized/infected patients in a dedicated ICU and total cohorting of nursing care and partial (daily shift only) cohorting of medical staff, the outbreak was controlled. According to the authors, cohorting was probably the most important contributing measure [123].

In a study by Lucet *et al.* patient cohorting was applied for surgical patients found to be ESBL-producing Enterobacteriaceae carriers, whereas in the other hospital units, CP alone were used. Pre-emptive isolation precautions were also recommended for patients transferred to the ICUs at risk of being colonized. The IPC measures were ineffective during the first year. The main cause was probably the low compliance rate with CP, despite a high rate of hand washing adherence. Critical evaluation of the implementation of CP in the ICU prompted corrective measures for CP and the incidence of acquired cases subsequently decreased [124]. This seems to suggest that auditing adherence to CP is at least as important an issue as their introduction per se.

Recommendations

Epidemic setting

Strong recommendation: Implement contact precautions (CP) for all patients colonized and/or infected with extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, multidrug-resistant (MDR)-*Klebsiella pneumoniae*, MDR-*Acinetobacter baumannii* (moderate level of evidence); and *Pseudomonas aeruginosa* (very low level of evidence)

Strong recommendation: Use alert code to identify promptly patients already known as colonized with ESBL-producing Enterobacteriaceae and MDR-*K. pneumoniae* at hospital/ward admission and perform screening and pre-emptive CP (moderate level of evidence)

Strong recommendation: Isolate colonized and infected patients in a single room to reduce the risk of acquisition of ESBL-producing Enterobacteriaceae, MDR-*K. pneumoniae* (moderate level of evidence); MDR-*A. baumannii* and MDR-*P. aeruginosa* (low level of evidence)

Strong recommendation: Cohort staff to reduce the risk of acquisition of MDR-*K. pneumoniae* (moderate level of evidence)

CP in endemic setting

Many interventions on MDR-GNB in endemic settings included CP [122,136,137] and many national and international guidance

documents and expert opinion publications recommend the systematic use of CP in the management of MDR-GNB in the endemic setting [5,6,138–140]. Rodriguez-Bano *et al.* [81] reported hospital-wide successful control of MDR-*A. baumannii* through a bundle strategy that included CP along with ASC, HH, education, environmental and HCWs' hand cultures, a strict environmental cleaning policy, and regular staff meetings with feedback of data. A significant correlation between implementation of CP and number of patients colonized or infected with *A. baumannii* was reported in a large French hospital [132] and, on a smaller scale, CP and ASC were successfully applied in a surgical setting to control the transmission of MDR-*A. baumannii* [141]. A significant reduction in endemic carbapenem-resistant *K. pneumoniae* (CRKP) was observed by Kochar *et al.* [122] through a multifaceted intervention including CP. In the same intervention, no decrease was observed in the isolation rates of *A. baumannii* and *P. aeruginosa*. In Germany, Vonberg *et al.* [142] reported their successful experience in a stable endemic situation, including many high-risk patients, applying CP and isolation room for all patients with MDR-GNB. These reports seem to suggest that CP may have a significant role in reducing MDR-GNB spread in the endemic setting, although CP was always included in a multifaceted approach and therefore its specific effectiveness is difficult to define.

Recommendations

Endemic setting

Strong recommendation: Implement contact precautions (CP) for all patients colonized with extended-spectrum β-lactamase (ESBL)-Enterobacteriaceae (with the exception of *Escherichia coli*), multidrug-resistant (MDR)–*Klebsiella pneumoniae*, MDR-*Acinetobacter baumannii*, and MDR-*Pseudomonas aeruginosa* (moderate level of evidence)

Strong recommendation: Use alert code to identify promptly patients already known as colonized with MDR-*A. baumannii* at hospital/ward admission and perform screening and pre-emptive CP (moderate level of evidence)

The Role of Active Screening Cultures to Prevent Spread

Active screening culture allows the early identification of patients with colonization due to MDR-GNB at hospital admission and/or during hospitalization in order to apply CP and reduce person-to-person spread. This is based on the well-established fact that a significant reservoir of MDR-GNB colonized patients in hospital will go undetected by relying on results from clinical specimens submitted for routine diagnostic testing [143–145].

Harris *et al.* [143] estimated that among patients admitted to medical and surgical ICUs, the proportion of undetected ESBL-producing *E. coli* and *Klebsiella* spp. was 69%. Importantly, among patients with both positive clinical and screening cultures, the latter were positive an average of 2.7 days earlier than the clinical cultures [143]. Maragakis *et al.* [144] reported an undetected ratio of MDR-*A. baumannii* of 50% among patients in ICU. A point prevalence study in three New York City ICUs revealed that 14 (39%) of 36 hospitalized patients had faecal colonization with CRKP. The majority (86%) of these patients were not identified by routine clinical cultures [145].

The proportion of clinically evident cases among carriers may vary according to the virulence of the organism, the susceptibility of the particular patient population studied, and quality of IPC measures, e.g. adherence to bundles. Studies examining the relationship between colonization and infection also depend on the sensitivity of the methods used to detect colonization. For example, it has been shown that it may be difficult to detect the carriage of *A. baumannii* by routine methods and that the best body site for screening has not been well determined [136]. In contrast, although the site of colonization for Enterobacteriaceae is better defined, various screening methods may differ in their sensitivity in identifying specific resistant mechanisms or phenotypes.

The natural history of MDR-GNB colonization and subsequent infection has not been well described and might differ depending on the organism, the host's features, and other factors. Corbella *et al.* [146] evaluated faecal colonization with MDR-*A. baumannii* in ICU patients and found that clinical infections due to these strains occurred more frequently in patients with, than without, previous faecal colonization. Contrasting results have been reported during an outbreak investigation, where the majority of ICU patients harbouring CRKP did not develop clinical disease during their hospitalization [125].

A recent clinical epidemiological investigation quantified the sensitivity of perianal/rectal surveillance cultures in detecting MDR-GNB bacteria and identified factors associated with false-negative surveillance culture results [147]. In this study, the sensitivity of perianal/rectal surveillance swabs for detecting MDR-GNB colonization was 78%. The percentage was higher than that reported in other studies, which ranged from 42% to 69% when only colonization of the rectal site

with non-*Acinetobacter* MDR-GN species was considered [148,149].

Since PCR-based approaches for screening of MDR-GNB are still at an early stage, culture-based methodologies for screening are the most reliable option and remain the most favourable in terms of capacity and costs. Techniques using conventional bacterial culture methods on agar plates for screening individuals for MDR-GNB are well-established. Adequate samples are usually rectal swabs, urine or respiratory secretions. HICPAC/CDC guidelines recommend taking ASC for MDR-GNB from areas of skin breakdown and draining wounds and, if a respiratory tract reservoir is suspected, from endotracheal tube aspirates or sputum. The Association for Professionals in Infection Control and Epidemiology (APIC) guide for the control of MDR-*A. baumannii* suggests culturing multiple patient sites including the nose, throat, axilla, groin, rectum, open wounds and/or tracheal aspirates (available from http://www.apic.org/resource_/eliminationguideform/b8b0b11f-1808-4615-890b-f652d116ba56/file/apic-ab-guide.pdf). Inoculation of the sample on non-selective media (Columbia Agar with 5% Sheep Blood; COS; BD, Franklin Lakes, NJ, USA) should be used as growth and internal quality control. For ESBL detection, inoculation on selective media (e.g. ESBL AgarchromID™ Agar; ESBL (bioMérieux, Marcy l'Etoile, France); Brilliance ESBL agar from Oxoid (Basingstoke, UK) and media containing 1 mg/L of cefotaxime or 4 mg/L of ceftazidime) may be used. MacConkey agar supplemented with 1 mg/L of imipenem may be used for the detection of carbapenamase-producing Enterobacteriaceae. The incubation period is a maximum of 48 h under aerobic conditions at 36°C. Only samples with concomitant growth on COS are considered 'valid' (note that this applies only to samples where growth of standard flora is expected, e.g. rectal swabs). Specimens should be identified and tested for antimicrobial susceptibility in a standardized way, e.g. according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Automated techniques may facilitate microbial identification (e.g. MALDI-TOF mass spectrometry) and antimicrobial susceptibility testing (e.g. Vitek2, BD Phoenix™, BD). The cost-effectiveness of these methods in different epidemiological setting needs to be further defined.

The frequency of screening is another key point for the implementation of ASC, but no consensus exists on the optimal timing and interval. ASC should be continued weekly until no cases of colonization or infection, suggesting ongoing cross-transmission, are identified [6]. A significant problem is also related to the lack of specific information related to the duration of colonization. Snyder *et al.* reported that the median duration of MDR-GNB colonization was 144 days (range, 41–349 days) ranging from 121 days in *Proteus* spp. to 178 days in *E. coli* [150].

In a study assessing the sensitivity of various anatomical sites for detecting baseline colonization with MDR-GNB, surveillance cultures from six different sites (groin, perirectal area, finger webs, forehead, axillae, toe webs) were performed. The groin was the most sensitive site with the highest negative predictive value for detecting MDR-GNB colonization, including MDR-*A. baumannii* and ESBL-producing *K. pneumoniae*. The perirectal area had the second highest sensitivity overall and was the most sensitive anatomic site for detecting ESBL-producing *E. coli*. Sampling of both perirectal and groin areas resulted in an increase of the overall sensitivity to 95% [151]. In another study, patients with recent clinical isolation (≤10 days) of MDR-*A. baumannii* and those with remote clinical isolation (≥6 months), were compared to determine optimal surveillance sampling sites. Screening for carriage was conducted from six sites: nostrils, pharynx, skin, rectum, wounds and endotracheal aspirates. Screening cultures yielded MDR-*A. baumannii* from 55% (12/22) of patients with recent clinical isolation, resulting in a sensitivity of 55% when six body sites were sampled. Sensitivities of single sites ranged from 13.5% to 29%, indicating that the sensitivity of surveillance cultures is low, even when six different body sites were sampled [152].

It is important to underline that the effects of ASC are related to the level of compliance to the intervention. As one would expect, use of audit cycles (sometimes termed process surveillance) to ensure that interventions are being performed correctly predict the chances of success. Before implementing ASC it is also important to clearly define which IPC interventions need to be applied in patients found to be positive and in others while awaiting screening results. The introduction of the screening per se cannot be considered an infection control measure. Careful planning should be elaborated together with the hospital laboratory considering, among other factors, local turnaround time and cost-effectiveness.

Specific plans should be defined in case of isolation of CRE. When identifying a previously unrecognized CRE, a point prevalence survey in high-risk areas should be performed. If CRE are detected from clinical cultures or from the point prevalence survey, active surveillance testing of patients with epidemiological links to a patient with CRE infection should be conducted (available from: http://ecdc.europa.eu/en/publications/Publications/110913_Risk_assessment_resistant_CPE.pdf).

Despite the increasing clinical relevance of MDR-GNB colonization among hospitalized patients and beneficial previous experiences with the control of MDR-Gram-positive bacteria, the question as to whether and when ASC should be performed to identify MDR-GNB colonized patients is still hotly debated. As yet, no internationally agreed guidelines have clearly defined how to organize and implement ASC for the

detection of colonization with MDR-GNB at hospital admission, although all advocate targeted screening of high-risk patients in endemic or outbreak settings.

In recent years hospitals in many countries have experienced increases in the rates of patients colonized by MDR-GNB at hospital admission. In a 6-year survey (1995–2000) in a French surgical ICU, the rates of ESBL-producing Enterobacteriaceae colonization or infection were 0.4 new cases per 100 admissions [136]. A study investigating colonization with *A. baumannii* reported that 58% of ASC collected from newly admitted patients in an ICU with an endemic situation were positive for MDR-*A. baumannii* [153].

Observational studies have identified risk factors for colonization due to MDR-GNB at hospital admission. These include: recent antibiotic usage, residency or recent travel in a country with high incidence of MDR-GNB, hospitalization in a healthcare facility where MDR-GNB are endemic, advanced age, dialysis and residency in long-term care facilities or nursing homes ([154], 23rd European Congress of Clinical Microbiology and Infectious Diseases, abstract eP 697).

To try to clarify the impact of ASC in controlling the spread of MDR-GNB within hospitalized patients, Harris *et al.* suggested two key variables to be determined locally: (i) organism-specific proportion of antibiotic resistance attributable to antibiotic usage and (ii) organism-specific attributable fraction due to patient-to-patient transmission. Defining these parameters would imply that cost-effectiveness studies could be performed locally and used by hospital epidemiologists to implement ASC accordingly [155]. However, as underlined by the authors, at the moment no accurate estimates of these parameters exist for any MDR-GNB in the non-outbreak setting. Determining these two components becomes even more difficult where there is a community reservoir or frequent inter-hospital transfers or re-admissions of colonized patients requiring their thorough epidemiological tracking and molecular typing of strains and determination of antimicrobial resistance elements.

ASC in an epidemic setting

Several studies have provided examples of the efficacy of the ASC included in a multifaceted strategy in outbreak settings. Enoch *et al.* [156] described the ineffectiveness of an approach that did not include identification of carriers with ASC in controlling an outbreak of MDR-*A. baumannii* that occurred in 2006 in a British teaching hospital. In a second phase, a partial ward closure with strict physical segregation of patients and barrier nursing along with the use of ASC (3 days a week) were introduced and these measures were effective in containing the outbreak. In the participating ICU, almost 5% of screened patients were found to be colonized with MDR-*A. baumannii*. ASC enabled earlier detection of colonization in 25% of these carriers, saving 1–6 days before the detection from a clinical sample [156]. Ben-David *et al.* described a hospital-wide outbreak of CRE that was controlled only after implementing an intervention that included the use of rectal screening at admission and then weekly thereafter, in addition to the measures taken in accordance with the national infection control programme [125]. Notably, 52% of patients were identified by use of ASC initially and 39% of CPs were applied based on results of ASCs [125]. In an ICU department in a hospital in Belgium in which routine screening (on the day of admission and biweekly) and CP failed to prevent and interrupt an outbreak of ESBL-producing *K. pneumoniae*, reinforced infection control measures, including daily screening, controlled the outbreak without major disruption of medical care [123].

Recommendations

Epidemic setting

Strong recommendation: Implement a programme of active screening culture at hospital admission followed by contact precautions to reduce the spread of extended-spectrum β-lactamase-producing Enterobacteriaceae, multidrug-resistant (MDR)-*Klebsiella pneumoniae*, MDR-*Acinetobacter baumannii* (moderate level of evidence); and MDR-*Pseudomonas aeruginosa* (very low level of evidence)

ASC in endemic setting

A 3-year prospective, controlled, quasi-experimental study in achieving the control of the spread of MDR-*A. baumannii* infection and colonization was conducted in an endemic setting and supported the utility of ASCs [157]. Following an increase in the rate of MDR-*A. baumannii* infection and colonization in ICUs and a coronary care unit, a multifaceted intervention lasting 24 months, was introduced. The bundle included: (i) implementation of enhanced CP; (ii) ASCs for MDR-*A. baumannii* (comprising tracheal aspirates and rectal swabs, on admission and then weekly; (iii) cohorting patients with MDR-*A. baumannii*, and (iv) enhanced environmental cleaning. Twenty-four months after the introduction of the multifaceted strategy, the rate of colonization had decreased by 76%. As several interventions were made simultaneously, it is impossible to establish which measure was the most effective [157]. A further verification of the efficacy of the use of ASCs in endemic settings was provided by Rodriguez-Bano *et al.* A multifaceted control programme to reduce MDR-*A. baumannii*

transmission included measures to improve adherence to HH, CP and ASC at hospital admission and weekly, implementation of environmental cleaning, and regular staff meetings. The bundle resulted in a sustained decrease in the rate of colonization and infection and of bacteraemia due to MDR-*A. baumannii* [81].

In contrast, Barbolla *et al.* reported that the introduction of ASC did not decrease cross-transmission of carbapenem-resistant *A. baumannii* (CRAB) in endemic setting. In this study oropharyngeal, axillary and rectal swabs were collected from all newly admitted ICU patients at admission and then weekly. CPs were applied in colonized and infected patients with no effect on the rate of MDR-GNB colonization [153].

The results of interventions are also related to the type of microorganism. A retrospective study, with pre- and post-interventional phases, was carried out by Kochar *et al.* [122]. In the first period, CP for MDR-GNB-colonized or -infected patients and ASC for CRAB at admission and weekly were introduced. In the second phase, ASC included the identification of CRKP and CR-*P. aeruginosa* (CRPA). Interestingly, the number of patients with CRAB or CRPA did not significantly differ in the two study periods, whereas there was a marked decrease in the number of patients with CRKP during the second period. Possible explanations for the lack of effect of ASC for *P. aeruginosa* and *A. baumannii* are either that these bacteria frequently colonize the respiratory tract, which was not included in their screening strategy, or that the patients were not efficient reservoirs for those microorganisms [122].

After evaluation of the evidence the authors of these guidelines agreed that the implementation of ASC should be suggested only as an additional measure and not included in the basic measures to control the spread of MDR-GNB in the endemic setting.

The Role of the Environmental Cleaning to Prevent Spread

Surface level cleanliness in healthcare environments has been shown to be important for controlling HAIs caused by Gram-positive microorganisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci and *Clostridium difficile* [158]. Studies that demonstrate the impact of cleaning alone for controlling GNB microorganisms other than *Acinetobacter* spp., however, are lacking, although environmental cleaning is often mentioned as part of an overall infection control package in response to an outbreak [158,159]. In many poorly controlled endemic situations, the healthcare environment has never been studied adequately and this may underestimate its importance. Although environmental screening has been performed to control outbreaks, its role remains contentious and the methodology has not been standardized [160]. Unexpected environmental reservoirs can sometimes be identified, suggesting that environmental screening should be considered, especially when control is not accomplished using basic IPC practices [134].

It is widely believed that coliforms and *Pseudomonas* cannot survive for long periods of time in dry healthcare environments and so do not pose as much of a threat as their more robust Gram-positive counterparts [161], although there are studies suggesting that the survival of coliforms and *P. aeruginosa* on dry surfaces might be longer than previously thought [162]. *Acinetobacter baumannii* can be recovered from the hospital environment with ease, including inanimate hand-touch sites near the patient [163]. Seeding clinical and environmental strains onto Formica surfaces demonstrated survival of between 1 and 2 weeks, although some strains are known to survive for much longer [164]. While *Acinetobacter* is known to survive in surface dust for months, organisms such as *E. coli*, *Klebsiella* spp., *Enterobacter* spp. and *Serratia* spp., have not generally demonstrated resilience to desiccation. However, recent reports suggest that GNB may actually display greater survival properties than Gram-positive organisms [162]. *Escherichia coli*, *Klebsiella* spp. and *Pseudomonas* spp. have all been shown to survive for more than a year under certain conditions, *Serratia marcescens* for up to 2 months and *Acinetobacter* spp. for up to 5 months [162]. *Pseudomonas* can survive on a dry floor for 5 weeks but little is known about *Burkholderia* and *Stenotrophomonas* persistence in the healthcare environment other than a predilection for biofilm lining sink traps and other plumbing components. In contrast, MRSA has been shown to survive for a year in hospital dust, the spores of *C. difficile* for 5 months and vancomycin-resistant enterococci for 4 months [162,165]. Environmental screening has recovered GNB from a variety of hospital surfaces. GNB have also been identified on general surfaces such as floors, shelves and ledges; curtains, linen, towels and clothes; mattresses and beds; furniture; computers, telephones and all items of clinical equipment [161,166–169]. Some pathogens, notably *Pseudomonas* spp., can survive well in damp places such as sinks, showers and baths. Dust-loving *A. baumannii* settles on rarely cleaned and/or inaccessible surfaces such as shelves, highly-placed equipment and computer keyboards; whereas coliforms such as *Klebsiella* and *Serratia* favour buckets, bowls, mops and liquids over dry surfaces [161,170].

A recent study examined a range of sites near patients known to be usually colonised by GNB [168]. Of nearly 2000 sites sampled, only about 5% demonstrated the presence of

isolates indistinguishable to those from the patient whose environment was sampled [168]. Organisms identified included *Pseudomonas*, *Stenotrophomonas maltophilia*, *E. coli*, *Enterobacter*, *Acinetobacter*, *Serratia* and *Klebsiella* spp. Sites more likely to host GNB included linen, gowns and nightwear; bedside tables, bed rails and chairs; floors and door handles; infusion pumps and respirators; and bathroom sites such as urinals, shower fittings, sinks and toilet seats.

Another study used standardized sampling methodology for ten hand-touch and general sites in different wards of a teaching hospital and confirmed that 5% of environmental sites were positive for GNB [171]. Coliforms, *Pseudomonas* spp. and *Stenotrophomonas maltophilia* were more often recovered from 'wet' sites such as sinks and baths, although there was a difference between the recovery rate of coliforms and pseudomonads from sinks on different wards. Very few coliforms were isolated from ICU sinks, as opposed to sinks on medical wards, and pseudomonads were isolated more frequently from ICU sinks than those on the medical wards. The authors attributed this to the frequent dispensing of disinfectants into the ICU sinks by staff engaged in hand disinfection, particularly products containing chlorhexidine and alcohol. All environmental GNB recovered from the ICU environment were significantly more resistant to antibiotics than those from the medical wards. The study concluded that antibiotic consumption is associated with resistance profiles of organisms on floors and other surfaces within a defined local environment such as a hospital ward [171].

Previous room occupancy by a GNB-colonized or GNB-infected patient has been shown to be a risk for acquisition of GNB [135]. There are several different methods for assessing both the efficacy of cleaning and the extent of environmental contamination in the hospital environment. Although more evidence for cleaning in control of HAI including MDR-GNB is still needed, it is generally agreed that maintaining a clean environment provides a fundamental basis for all hygienic measures in preventing infection [158]. GNB can survive on hospital surfaces and studies have demonstrated strains that are indistinguishable from both environmental reservoirs and patients [172]. Given the potential role of cleaning in the control of MDR-GNB, therefore, methods for assessing cleanliness are needed, both for scientific studies and to reassure staff and patients. Such methods can be defined within two main categories: process evaluation, where the cleaning process is monitored by visual inspection or with a fluorescent gel marker; and outcome evaluation, where cleanliness is evaluated with the use of ATP bioluminescence systems or microbial cultures [173].

Either fluorescent markers or kits for measuring organic soil have confirmed that many high-risk sites escape appropriate cleaning. Auditing surfaces and equipment on a ward can establish what is handled, how often it is handled and who has cleaning responsibility. The results of these audits provide basic information for manipulation of cleaning schedules, although cleaning responsibilities and resources for any extra cleaning hours require robust managerial support. There are alternative methods of environmental assessment, notably cleaning inspections; education; monitoring and feedback, all of which encourage enhanced performance by housekeepers. Placing invisible fluorescent markers at key sites for later inspection and feedback for domestic staff has also been shown to improve overall cleaning compliance, along with reduction of key hospital pathogens. Use of ATP monitoring demonstrates pronounced effect on cleaners when they received concomitant educational guidance. Direct observation and supervision of staff as they clean also demonstrates reductions of important hospital pathogens on high-risk surfaces [158].

Organisms from water outlets have the potential to colonize and infect patients despite the lack of evidence for specific transmission pathways. Outbreaks of *P. aeruginosa* and *Stenotrophomonas maltophilia* have been traced to tap filters and aerators, sink traps and drains, usually hosting adherent biofilms [174]. Sinks form a reservoir for many different GNB [170,174–181]. Biofilms also build up in sink traps underneath the outlet. This complex living deposit on internal plumbing surfaces hosts and protects a multitude of water-loving organisms, some of which pose a threat to nearby debilitated patients. In addition, bacteria within biofilms may display greater capacity for antimicrobial resistance and can tolerate chlorine and other disinfectants [182]. Biofilm-forming *K. pneumoniae* strains are also more likely to produce ESBLs [183].

It is not known to what extent sink usage for HH, etc. encourages sink contamination or aerosolization from backsplash, but investigation of pathogens from sinks, surrounding surfaces and patient isolates have demonstrated indistinguishable strains [170,174,175]. Disinfection using chlorinated products, without disruption of biofilm, only offers limited control; a comprehensive cleaning initiative is required to physically remove the biofilm lining the surfaces of affected plumbing components [174,184]. These are often difficult to access and require close collaboration between personnel with hospital engineering and construction expertise.

Detergent-based cleaning might remove microbes, but will not necessarily kill them [10]. Disinfectants are more effective at killing pathogens than detergents but some hospital pathogens can resist the bactericidal effect of particular agents due to a number of resistance mechanisms [185,186]. Potential cross-resistance between biocides and antimicrobial agents should also be considered. No one single process will remove

all relevant microbial soil from the hospital, despite innovative products containing both detergent and disinfectant products. There is substantial uncertainty regarding the impact of use of specific disinfectants in the hospital environment, because laboratory testing does not necessarily predict what actually happens on hospital surfaces. Physical removal may be as effective as using disinfectants for controlling environmental microbes. MDR-*Serratia marcescens* can survive in chlorhexidine and *Stenotrophomonas* spp. have been linked with deionized water used for diluting 'Savlon'™ concentrates containing chlorhexidine (1–5%) and cetrimide (15%) [186]. Spray cleaning fluids can also become contaminated with GNB, including *Enterobacter cloacae*, *Acinetobacter*, *Klebsiella* and *Pseudomonas* spp. [187,188]. Eight out of ten samples from alcohol-containing cleaning fluids in daily hospital use were contaminated with various GNB (mainly *Pseudomonas* spp.) [188]. Failure to clean the spray containers properly on a daily basis meant that domestic staff were effectively spraying the hospital floors with a culture of *Pseudomonas* spp. Cleaning equipment may also become contaminated with hospital pathogens and disperse these into the hospital environment [161,189,190].

Innovative forms of cleaning and decontamination methods for the healthcare environment are constantly appearing [158]. These have an impact on all environmental pathogens, including spore-forming bacilli, but robust evidence supporting their use for the control of MDR-GNB is lacking. There are novel disinfectants such as electrolysed water, and automated systems dispelling steam, hydrogen peroxide, ozone and different types of UV light. Studies to evaluate the impact of antimicrobial surfaces, such as steel, copper, silver and nano-silver particles combined with light-activated titanium dioxide have demonstrated equivocal results on environmental contamination [191–196]. However, traditional cleaning methods should not be relaxed or abandoned even if new cleaning systems are introduced as problems have occurred with some of the methods mentioned [191,197–208].

EC in epidemic setting

The best evidence for cleaning is found in the studies on the prevention or control of outbreaks of *Acinetobacter* spp. [209–211]. One study provided a strong indication for the role of cleaning during an outbreak caused by MDR-*A. baumannii* involving more than 30 patients in two ICUs [209]. ICU environmental contamination was recognized as an important reservoir for this epidemic strain. The outbreak ceased only after the ICUs were closed for complete cleaning and disinfection. Another study examined the levels of environmental contamination with *A. baumannii* in a neurosurgical ICU during a prolonged outbreak [163]. As with MRSA and *C. difficile*, there were many near-patient hand-touch sites that yielded the epidemic strain. This study also demonstrated a significant association between the amount of environmental contamination and patient colonization. The conclusion was that high standards of cleaning play an integral role in controlling outbreaks of *Acinetobacter* in the ICU.

Acinetobacter can also be a persistent problem for burn patients [212]. Following an increase in *Acinetobacter* infection rates among paediatric burns patients, an environmental screening programme recovered the organism from various surfaces in the patients' rooms including the plastic covers shielding the bedside computer keyboards. IPC measures that included donning of gloves before using computers and thorough disinfection of these plastic covers effectively terminated the outbreak [212].

Although environmental cleaning interventions have been performed mainly to control outbreaks due to MDR-*A. baumannii*—albeit with controversial results—the literature also includes reports of outbreaks of coliforms, pseudomonads and *Stenotrophomonas* spp. traced to discrete pieces of equipment, environmental sites or possibly specific cleaning practice failures [151,161]. Identification and eradication of the reservoir appeared to terminate the various outbreaks caused by a wide range of MDR-GNB [170,174–181,189,213,214]. The interventions have been many and some involved the introduction or changing of a cleaning regimen or complete removal of one or more suspected items of equipment.

Recommendations

Epidemic setting

Strong recommendation: Monitor cleaning performance to ensure consistent environmental cleaning (EC). Vacate units for intensive cleaning. Implement regular EC procedures and, when available, dedicate non-critical medical items for use on individual patients colonized or infected with extended-spectrum β-lactamase Enterobacteriaceae and multidrug-resistant-*Acinetobacter baumannii* (moderate level of evidence)

EC in endemic setting

There is little evidence for the role of cleaning for controlling MDR-GNB in situations other than those of outbreaks [215,216]. Staff working in an 11-bed ICU received an educational intervention to improve HH and EC [217]. This resulted in a decrease in the number of patients colonized with ESBL-Enterobacteriaceae from 70% during a 3-month pre-intervention period to 40% during a post-intervention period. This study was

uncontrolled, however, comprised two interventions, and it is possible that the initial high proportion of colonized patients actually represented an underlying outbreak [217].

Interventions including EC and removal of potentially contaminated equipment as components of a bundle of IPC practices were performed in endemic settings for MDR-*A. baumannii* [212,214], ESBL-producing GNB [213] and MDR-*K. pneumoniae* [179] but with different results. Following the identification of a CRKP in a district general hospital in the UK, cleaning of the ward using a chlorine-based agent was carried out and patient-related items were cleaned at least once a day by nursing staff [218]. Enhanced cleaning was only part of the overall infection control package, however, along with the use of a urinary catheter care bundle; patient note tagging; HH emphasis; and CP for patient cases.

Recommendations

Endemic setting

Strong recommendation: Implement regular environmental cleaning (EC) procedures and, when available, dedicate non-critical medical items for use on individual patients colonized or infected with multidrug-resistant-*Acinetobacter baumannii* (moderate level of evidence)

The Role of Antimicrobial Stewardship to Prevent Spread

Numerous papers have demonstrated that previous antimicrobial drug exposure is a strong risk factor for colonization and infection due to drug-resistant bacteria [219–222]. Fluoroquinolones and third-generation cephalosporins have often been implicated in promoting the spread of MDR-bacteria [220–222], although, the direct association between antibiotic therapy and the acquisition of antibiotic-resistant bacteria is still unclear. The studies are often confounded by scarce data on antibiotic usage and differ according to microorganism, dosage, drug combinations, timing of exposure and setting. A recent Cochrane systematic review showed that interventions to reduce excessive antibiotic prescribing to hospital inpatients can reduce antimicrobial resistance or hospital-acquired infections and interventions to increase effective prescribing can improve clinical outcome [223].

One of the earlier illustrations of the efficacy of antibiotic intervention is the work by Gerding *et al*. who, to address high rates of gentamicin resistance among GNB, substituted amikacin for gentamicin in the hospital formulary at two separate points in a 10-year time period at the Minneapolis Veterans Affairs Medical Center [224]. A retrospective review of this 10-year period revealed a significant decline in the rate of gentamicin resistance among GNB following each substitution.

More recently, Ntagiopoulos *et al.* investigated the influence of an antibiotic policy programme based on the restriction of the empirical use of fluoroquinolones and ceftazidime on the susceptibilities of GNB in a general ICU in Greece. After a 24-month period of protocol application, consumption of both restricted antibiotics and antibiotics in general were reduced by 92% and 55%, respectively. Susceptibilities to ciprofloxacin of the three predominant infection-causing GNB increased significantly. No differences were observed in overall mortality and type of infections between colonizing and infecting strains [225].

In another study from Turkey, a nationwide antibiotic restriction programme was evaluated for its effect on antibiotic consumption, antimicrobial resistance and costs. The data obtained from four university hospitals, and one referral tertiary-care educational state hospital were included in the analysis. Antimicrobial resistance profiles of 14 233 selected microorganisms causing bacteraemia and antibiotic consumption were analysed, retrospectively. A negative correlation was observed between ceftriaxone consumption and the prevalence of ceftriaxone-resistant *E. coli* and *Klebsiella* spp. The decreased usage of carbapenems was correlated with decreased CRPA and CRAB [226].

Interesting studies on the impact of an ABS programme on antimicrobial resistance were those performed to reduce the morbidity of *C. difficile* diarrhoea. In a study by Malani *et al.* [227] in which there was a review of 510 antimicrobial orders, implementation of an ABS programme was associated with a 50% reduction in the likelihood of developing *C. difficile* infection, and with a 25.4% drop in defined daily doses of the target antimicrobials. There is also increasing evidence to suggest that appropriate antibiotic use can decrease the incidence of MDR-GNB [228,229], even though data are controversial [230].

There are different approaches to the control and limiting of antibiotics consumption in hospitalized patients. Antibiotic restriction, i.e. the requirement for approval of the antibiotic from an infectious diseases specialist might be one of the most effective control methods [231,232]. A variety of such use-justification approaches have been designed to improve antibiotic use. These have included telephone approval from an infectious diseases specialist, automatic stop orders, and antibiotic order forms that require justification for the prescribed drug after dispensing from the pharmacy. At the Indiana University Medical Center a prior approval programme resulted in decreased

enterococcal and GNB bacteraemia as well as fewer infections due to *Stenotrophomonas maltophilia* and MRSA [233].

Kollef *et al.* [234] studied the effects of a scheduled change in empiric antibiotic coverage of suspected GNB infection from ceftazidime to ciprofloxacin in 680 patients who had undergone cardiac surgery during two 6-month periods. The study revealed a significant reduction of 42% in the incidence of ventilator-associated pneumonia, presumably as the result of a significant reduction in pneumonia caused by MDR-GNB. Additionally Kollef *et al.* were able to demonstrate improved antibiotic susceptibility profiles for Gram-negative isolates (49% resistant before intervention versus 20% after) but did not demonstrate a difference in crude mortality (5% versus 8%) or mortality attributed to ventilator-associated pneumonia caused by MDR-GNB [234].

Antibiotic cycling or rotating (i.e. the scheduled alternation of various classes of antibiotics) has been described as an important strategy for decreasing resistance. The goal of antibiotic cycling or rotation is a sustainable decline or stabilization in antimicrobial resistance through successive, prospective alterations in antibiotic selection pressures that prevent the selection of specific resistance traits and hence, organisms. Indeed, cycling of antibiotics in high-risk units can successfully modify resistance patterns and the concept of cycling is theoretically compelling [235,236]. Its usefulness, however, may be limited because of concerns about practical applicability and the durability of resistance genes [237,238]. Important unresolved issues include determining the superiority of site-specific versus organism-specific rotation strategies, optimal duration of rotation periods, types of antibiotics used and in what order, and analysis of the transmissibility of resistance elements in the various clones on the units. Additional issues relate to whether rotation could be effective also in units with low rates of resistance and if it is possible to measure the 'optimal density of antibiotic use' (i.e. number of doses/patient admissions or days) that could be used to guide formulation of rotation strategies [239].

The implementation of antibiotic guidelines or protocols has been shown to be a formal means of achieving the goals of appropriate antibiotic use, limiting unnecessary antibiotic use and, as a result, improving antibiotic susceptibility profiles [240]. Computer software has the potential to assist in the appropriate choice of antibiotics. Although computerized decision-support systems are not available at many institutions, they should be considered as a paradigm for the design of other computer-based interventions [241,242]. In an Australian ICU the impact of the implementation of a computerized antibiotic decision support was assessed over a 7-year period on the resistance patterns of the most common clinically isolated GNB. The authors reported a significant improvement in susceptibility of *P. aeruginosa* to imipenem (18% per year) and gentamicin (12% per year) compared with the pre-intervention trend. Significant changes in the rates of gentamicin and ciprofloxacin susceptibility were also observed in the inducible Enterobacteriaceae group, although these were less clinically significant [243].

One of the major issues when planning an intervention to reduce inappropriate usage of antibiotics within healthcare facilities is that clinical studies have often been limited by selection biases, small sample sizes, limitation to single institutions, inadequate pre-observation and post-observation datum points, and failure to deal with confounders. As pointed out by McGowan and Tenover, studies that demonstrate improved susceptibilities following a reduction in antibiotic use should be confirmed through multicentre prospective trials that adjust for common confounding factors, especially heightened IPC efforts and biases [244].

The aforementioned strategies can be incorporated into comprehensive programmes, designed to optimize antimicrobial therapy, to improve patient outcomes, ensure cost-effective therapy and reduce the adverse effects associated with antimicrobial use, including antimicrobial resistance. However, a few studies included in their outcomes the evaluation of the impact of an ABS programme on the resistance rate levels. When ABS is implemented in response to the emergence of resistance in a facility, in a multifaceted intervention, it is difficult to determine exactly what resulted in the decrease in the emergence of resistance.

ABS in epidemic setting

A broad programme of restriction of selected antibiotics was implemented at a large urban teaching hospital in Houston, Texas, USA after an outbreak of a highly resistant *A. baumannii* [245]. Prior authorization from the Infectious Disease Service was required before orders for amikacin, ceftazidime, ciprofloxacin and ticarcillin/clavulanate were filled by the pharmacy. Ceftriaxone use was not restricted and its use increased. As a result of the restriction programme, susceptibility rates to all β-lactam and quinolone antibiotics increased, with the greatest improvements seen in the areas of highest use. It is not clear why ceftriaxone susceptibility improved despite its increased use. A computerized programme to restrict third-generation cephalosporin use was introduced for a period of 9 months in a 750-bed university hospital in Korea where a sudden hospital-wide increase of ESBL-producing *K. pneumoniae* was detected. This system automatically stopped the prescription of these antibiotics if an infectious disease specialist did not approve the prescrip-

tion. Third-generation cephalosporin use decreased significantly whereas use of carbapenems and β-lactam/β-lactamase inhibitors increased from pre-intervention to intervention periods. The proportion of ESBL-producing *K. pneumoniae* isolates increased significantly from 8.1% in the pre-intervention period to 32.0% of intervention, and then decreased again to 20.6% during a further 9 months of post-intervention. Interestingly, no significant increase in the proportion of imipenem and piperacillin-tazobactam resistance among *P. aeruginosa* and *A. baumannii* was observed. The most important limitation of the study was the lack of consistency in assessing the cause–effect relationship between antibiotic restriction and resistance proportions due to the statistical model (before–after study instead of interrupted time series) and lack of adjustment for confounders [246].

Recommendations

Epidemic setting

Strong recommendation: Implement an antimicrobial stewardship programme. Plan interventions of restriction of antibiotic usage to reduce the spread of extended-spectrum β-lactamase-producing Enterobacteriaceae (moderate level of evidence)

ABS in endemic setting

Lautenbach *et al.* [247], in a study performed at two hospitals within the University of Pennsylvania Health System, observed that the association between previous quinolone use and fluoroquinolone-resistant *E. coli* colonization varied significantly by study year, suggesting that the clinical epidemiology of resistant organisms may have changed over time. No substantive changes were reported in the antimicrobial formulary or IPC protocols in the two study hospitals during the investigation. A 5-year quasi-experimental study was conducted in two hospitals to examine variations across hospitals in the response to antimicrobial interventions (i.e. restriction of ceftazidime and ceftriaxone) designed to curb the spread of ESBL-producing *E. coli* and *K. pneumoniae*. After the interventions, the prevalence of ESBL-producing bacteria decreased by different degrees in the two centres. The effect of antimicrobial formulary interventions seemed to vary substantially across institutions, perhaps as a result of differences in patient populations. The results suggest variability in the epidemiological profiles of ESBL-positive isolates at different hospitals [247]. A time-series analysis showed a temporal relationship between antimicrobial use and resistance [248]. Restriction of cephalosporins was associated with a decrease in the rate of cephalosporin-resistant *Klebsiella* species by 44% [249,250] and a 69% increase in imipenem resistance among *P. aeruginosa*. Under these circumstances, an open formulary could have prevented the dominant use of a single class of antibiotics and the emergence of resistance to that class, a phenomenon dubbed 'squeezing the resistance balloon' by Burke [251]. Rahal *et al.* concluded that antibiotic formulary restriction may positively affect antimicrobial susceptibility patterns, but alone it may also decrease the heterogeneity of antibiotic use and, consequently, enhance resistance. The investigators, therefore, postulated later that 'the resistance balloon can and should be squeezed at multiple sites' [252].

Recommendations

Endemic setting

Strong recommendation: Implement an antimicrobial stewardship programme to reduce the spread of extended-spectrum β-lactamase-producing Enterobacteriaceae (moderate level of evidence)

The Role of Decolonization and Topical Chlorhexidine to Reduce Spread

Decolonization regimens have been extensively studied in patients colonized with MRSA while only a few clinical trials focused on ESBL-producing Enterobacteriaceae [24,136,253–255]. Recently the first randomized, placebo-controlled clinical trial has been conducted in Switzerland to evaluate the efficacy of a systematic ESBL-producing Enterobacteriaceae eradication strategy including colistin sulphate (50 mg four times daily) and neomycin sulphate (250 mg four times daily) for 10 days plus nitrofurantoin (100 mg three times daily) for 5 days. Among 54 patients included in the primary analysis, there was no statistically significant difference between the groups with regard to the detection of ESBL-producing Enterobacteriaceae by rectal swab 28+7 days after the end of treatment. The regimen temporarily suppressed ESBL-producing Enterobacteriaceae carriage, but had no long-term effect.

Saidel-Odes *et al.* performed a randomized placebo-controlled trial using oral gentamicin and polymyxin E gel (0.5 g four times daily) plus oral solutions of gentamicin (80 mg four times daily) and polymyxin E (1×10^6 units four times daily) for 7 days to eradicate CRKP oropharyngeal and gastrointestinal carriage. The percentages of rectal cultures that were

negative for CRKP were significantly reduced at 2 weeks (16.1% in the placebo arm versus 61.1% in the decolonization arm; OR = 0.13; 95% CI, 0.02–0.74) while the reduction at week 6 (33.3% versus 58.5%) was not significant [256].

Available evidence does not enable the authors of these guidelines to provide recommendations on the usage of decolonization protocols to limit the spread of MDR-GNB among hospitalized patients. Further studies are needed to define the microbiological target, patient populations, and risk of development of resistance.

Chlorhexidine gluconate is an antiseptic agent with broad antimicrobial activity. Daily bathing of patients with chlorhexidine has been used to decrease the burden of VRE on patients' skin, HCWs' hands and environmental surfaces, and observational studies have demonstrated decreased risks for MRSA acquisition associated with routine cleansing of ICU patients with chlorhexidine [257]. Two recently published cluster-randomized studies assessed the impact of strategies involving daily cleansing of ICU patients with 2% chlorhexidine gluconate-impregnated bathing cloths [258,259]. Although both studies demonstrated a significant reduction in ICU-associated bloodstream infection rates associated with universal chlorhexidine cleansing, Climo *et al.* did not find a statistically significant impact on bloodstream infections due to GNB and Huang *et al.* did not specifically assess Gram-negative bloodstream infection risk [258,259]. Although chlorhexidine bathing has also been used as a strategy to prevent acquisition of MDR-GNB in both the endemic and outbreak settings, the few studies that have evaluated the impact of chlorhexidine bathing on MDR-GNB have been single-centre, observational studies, and often include other simultaneously implemented interventions aimed at preventing MDR-GNB transmission. One study assessed the impact of daily bathing of patients admitted to a trauma centre's ICU with 2% chlorhexidine gluconate-impregnated bathing cloths, and found a non-statistically significant decrease in risk for colonization with *A. baumannii* [260]. Daily bathing with 2% chlorhexidine has also been used as one component of successful bundled interventions used to control outbreaks of CRKP in long-term acute care hospitals and ICUs [261,262].

Reduced susceptibility to chlorhexidine has been reported among GNB [263], so sustained use of topical chlorhexidine as a strategy to limit transmission of MDR-GNB should ideally be accompanied by surveillance for the emergence of chlorhexidine resistance over time.

Available evidence does not enable the authors to derive strong recommendations for the wide application of chlorhexidine in hospitalized patients colonized or infected with MDR-GNB.

The Role of Infrastructure and Education to Reduce the Spread

A few papers included improvement of infrastructure in a multifaceted approach to reduce the spread of MDR-GNB. The most interesting example was reported from Israel where the authors controlled a national outbreak of MDR-*K. pneumoniae* with a multifaceted approach including contact isolation measures and placement of patients carrying CRE in self-contained nursing units staffed by dedicated nurses, and isolation of known carriers at subsequent hospitalization. Importantly, mandatory reporting to public health authorities of every CRE patient and mandatory isolation of those hospitalized were introduced. Furthermore, compliance with isolation measures was monitored throughout the country by a central authority. Finally a Task Force on Antimicrobial Resistance and Infection Control was created that reported directly to the Ministry of Health Deputy Director-General. The task force was invested with the statutory authority to intervene as necessary to contain the outbreak [127]. Although limited evidence was available for such a generalization, the authors conclude that administrative support, including economic and human resources, was essential to prevent and control MDR-GNB at a global level.

Public health resources should support the initiation of IPC interventions within hospitals. An IPC infrastructure should include environmental personnel, such as estates, domestic and janitorial representatives. National health programmes should include a specific economic plan to support hospitals with high-endemic MDR-GNB, providing resources for adequate staffing and training. The local application of IPC measures should be supported by management of the healthcare facility by providing administrative and financial resources (World Health Organization. Available at http://www.who.int/csr/resources/publications/WHO_HSE_EPR_2009_1/en/).

Education becomes even more important as a key core component to help reduce the transmission of MDR-GNB in endemic or epidemic settings. There have been many interventions to reinforce HCWs' knowledge of the importance of IPC in outbreak settings. These have included educational programmes ranging from local-unit to hospital-wide training and from a few modules to daily staff meetings. Regular education meetings held every 2–4 weeks with physicians, nurses, physical therapists and students working in affected areas were part of an effective bundle used to control endemic *A. baumannii* in one study [81]. Diverse groups of practitioners and professionals, i.e. doctors, nurses, respiratory technicians, pharmacists and environmental service personnel need to be

educated on core components of infection prevention and the pivotal role that these play in preventing transmission of MDR-GNB. In a study conducted in a mixed ICU of an American 300-bed tertiary-care hospital, meetings were held with the infection control and nursing staff to encourage strict adherence to the ICP measures, including rectal surveillance cultures, extensive EC and cohorting patients and staff. The combined intervention was effective in reducing the incidence of endemic CRKP [122]. During an outbreak of ESBL-producing *K. pneumoniae*, every day meetings between the ICU and infection control teams were held to reinforce infarction control measures previously failing to control the epidemic. This intervention included in a multifaceted approach controlled the outbreak in 50 days [123].

Inter-professional education should facilitate learning new practices together in a team setting, increasing likelihood of uptake of the new practice behaviours, and greater understanding of team member roles. In particular, evidence-based interventions, combined with adaptive strategies and behaviour change management processes, could help the healthcare team to produce state-of-the-art infection prevention practices.

Recommendations

Epidemic setting

Strong recommendation: Conduct educational programmes to ensure that healthcare workers understand why extended-spectrum β-lactamase-Enterobacteriaceae are important epidemiologically, why prevention of spread is critical for control, and which measures for preventing spread have proven to be effective (moderate level of evidence)

Endemic setting

Strong recommendation: Conduct educational programmes to ensure that healthcare workers understand why multidrug-resistant-*Acinetobacter baumannii* is important epidemiologically, why prevention of spread is critical for control, and which measures for preventing spread have proven to be effective (moderate level of evidence)

Recommendations

Recommendations are presented according to epidemiological setting (endemic versus epidemic situations) and differentiated into: 'basic' practices recommended for all acute-care facilities, and 'additional special approaches' to be considered when there is still clinical and/or epidemiological and/or molecular evidence of ongoing transmission regardless of the application of these basic measures. Hospitals should consider adopting one or more of these additional measures according to the local epidemiology and patients' comorbidities.

The evidence on basic practices was extracted from literature that had mainly reported the control of hospital spread of MDR-GNB in 'endemic' situations, whereas the evidence for the additional measures was mainly taken from 'outbreak' control reports. Recommendations are presented according to endemic and epidemic situations (see Table 1 for definitions), as literature differed in strategies shown to be effective, according to the situation and are also presented, where possible, by MDR-GNB type. When the evidence was derived from studies not providing results by type of microorganism, the level of evidence and recommendations are provided referring to MDR-GNB. The level of evidence (very low/low/moderate/strong) and strength of recommendation (conditional/strong) are defined according to the GRADE approach (available from: http://www.gradeworkinggroup.org). Where the level of evidence and recommendations are not provided it means that no scientific evidence was available.

Tables 2 and 3 illustrate the GRADE approach and specific definitions for determinants of quality and evidence that were applied to extract the final recommendation. The cumulative level of the evidence stratified by microorganisms and type of intervention is shown in Tables 4–9.

The authors would like to point out that the revision of evidence clearly shows 'grey' areas where studies with appropriate design are urgently needed: CP for high-risk patients (i.e. haematological or ICU patients) colonized or infected with ESBL-producing *E. coli*, cohorting of patients and staff, and ABS programme. The authors also underline that since the current review was not able to produce specific indications stratified by patients' risk, because of the lack of evidence, the application of these guidelines to high-risk patients, e.g. ICU patients, burn patients, or haematological patients, should be carefully locally evaluated according to ecology and patients' comorbidities.

TABLE 4. Quality of studies by intervention. Basic measures to reduce the spread of multidrug-resistant (MDR)-*Klebsiella pneumoniae* and extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae in hospitalized adult patients: recommended for all acute-care facilities in endemic setting

Microorganism	MDR-*K. pneumoniae*				ESBL-producing Enterobacteriaceae			
	Quality of studies [ref.]			Overall quality of evidence	Quality of studies [ref.]			Overall quality of evidence
Intervention	Moderate	Low	Very low		Moderate	Low	Very low	
Hand hygiene	2 [122,265]	–	–	Moderate	2 [137,266]	1 [267]	–	Moderate
Education	1 [122]	–	–	Moderate	1 [266]	1 [267]	–	Moderate
Contact precautions	2 [122,265]	–	–	Moderate	3 [136,137,266]	1 [267]	–	Moderate
Isolation room	1 [265]	–	–	Moderate	1 [137]	1 [267]	–	Moderate
Environmental cleaning	2 [122,265]	–	–	Moderate	1 [137]	–	–	Moderate
Antimicrobial stewardship	1 [268]	1 [269]	–	Moderate	4 [136,268,270,271]	2 [267,272]	1 [273]	Moderate

TABLE 5. Quality of studies by intervention. Basic measures to reduce the spread of multidrug-resistant (MDR)-*Acinetobacter baumannii* and MDR-*Pseudomonas aeruginosa* in hospitalized adult patients: recommended for all acute-care facilities in endemic setting

Microorganism	MDR-*A. baumannii*				MDR-*P. aeruginosa*			
	Quality of studies			Overall quality of evidence	Quality of studies			Overall quality of evidence
Intervention	Moderate	Low	Very low		Moderate	Low	Very low	
Hand hygiene	4 [81,122,153,157]	1 [274]	–	Moderate	2 [122,275]	1 [274]	–	Moderate
Education	4 [81,122,153,157]	1 [274]	–	Moderate	1 [122]	1 [274]	–	Moderate
Contact precautions	4 [81,122,153,157]	–	–	Moderate	1 [122]	–	–	Moderate
Isolation room	1 [81]	–	–	Moderate	–	–	–	Insufficient
Environmental cleaning	4 [81,122,153,157]	–	–	Moderate	1 [122]	–	–	Moderate
Antimicrobial stewardship	1 [268]	2 [269,272]	–	Moderate	2 [268,275]	2 [269,272]	–	Moderate

TABLE 6. Quality of studies by intervention. Basic measures to reduce the spread of *Stenotrophomonas maltophilia* and *Burkholderia cepacia* in hospitalized adult patients: recommended for all acute-care facilities in endemic setting

Microorganism	*S. maltophilia*				*B. cepacia*			
	Quality of studies			Overall quality of evidence	Quality of studies			Overall quality of evidence
Intervention	Moderate	Low	Very low		Moderate	Low	Very low	
Hand hygiene	–	–	–	Insufficient	–	–	–	Insufficient
Education	–	–	–	Insufficient	–	–	–	Insufficient
Contact precautions	–	–	–	Insufficient	–	–	–	Insufficient
Isolation room	–	–	–	Insufficient	–	–	–	Insufficient
Environmental cleaning	–	–	–	Insufficient	–	–	–	Insufficient
Antimicrobial stewardship	–	1 [272]	–	Low	–	–	–	Insufficient

TABLE 7. **Quality of studies by intervention. Basic and additional measures to reduce the spread of multidrug-resistant (MDR)-*Klebsiella pneumoniae* and extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae in hospitalized adult patients: recommended for all acute-care facilities in epidemic setting**

Microorganism	MDR-*K. pneumoniae*				ESBL-producing Enterobacteriaceae			
	Quality of studies			Overall quality of evidence	Quality of studies			Overall qualityof evidence
Intervention	Moderate	Low	Very low		Moderate	Low	Very low	
Hand hygiene	–	–	3 [276–278]	Very low	3 [123,124,279]	5 [48,280–283]	3 [62,217,284]	Moderate
Education	1 [126]	2 [285,286]	2 [277,278]	Moderate	3 [123,124,279]	5 [48,128,281,282,288]	1 [217]	Moderate
Active surveillance cultures	2 [125,126]	2 [286,287]	2 [277,278]	Moderate	2 [123,124]	5 [48,128,264,280,281]	1 [217]	Moderate
Healthcare workers screening	–	–	–	Insufficient	–	2 [128,280]	1 [62]	Low
Contact precautions	3 [125–127]	3 [285–287]	3 [276–278]	Moderate	3 [123,124,279]	6 [48,128,264,281–283]	3 [62,217,284]	Moderate
Isolation room	2 [126,127]	3 [285–287]	1 [278]	Moderate	3 [123,124,279]	4 [128,280,281,283]	2 [62,284]	Moderate
Pre-emptive CP/alert code	3 [125–127]	–	1 [278]	Moderate	2 [123,124]	2 [280,281]	–	Moderate
Cohort patients	2 [126,127]	1 [285]	2 [277,278]	Moderate	1 [123]	5 [48,128,281–283]	–	Moderate
Cohort staff	2 [126,127]	2 [285,287]	2 [277,278]	Moderate	1 [123]	1 [128]	–	Moderate
Environmental cleaning	1 [126]	1 [285]	1 [278]	Moderate	2 [123,279]	6 [48,128,264,280,281,283]	2 [217,284]	Moderate
Environmental screening	–	1 [285]	–	Low	1 [279]	3 [48,264,280]	1 [62]	Moderate
Antimicrobial stewardship	–	–	3 [276–278]	Very low	2 [123,246]	3 [281,282,288]	1 [284]	Moderate

CP, contact precautions.

TABLE 8. **Quality of studies by intervention. Basic and additional measures to reduce the spread of multidrug-resistant (MDR)-*Acinetobacter baumannii* and MDR-*Pseudomonas aeruginosa* in hospitalized adult patients: recommended for all acute-care facilities in epidemic setting**

Microorganism	MDR-*A. baumannii* Quality of studies			Overall quality of evidence	MDR-*P. aeruginosa* Quality of studies			Overall quality of evidence
Intervention	Moderate	Low	Very low		Moderate	Low	Very low	
Hand hygiene	1 [289]	9 [129,131,134, 214,290–294]	10 [130,295–303]	Moderate	–	2 [304,305]	3 [306–308]	Very low
Education	2 [289,309]	7 [129,131,134, 156,290,293,294]	4 [297,299,302,310]	Moderate	–	–	2 [306,307]	Very low
Active surveillance cultures	1 [309]	6 [129,131,156, 292,294,311]	2 [141,298]	Moderate	–	–	2 [306,308]	Very low
Healthcare workers screening	–	5 [129,131,214, 290,294]	6 [297–299,301, 302,310]	Very low	–	–	–	Insufficient
Contact precautions	2 [289,309]	11 [129,131,134,1 56,214,290–294,311]	12 [130,141,295–303, 310]	Moderate	–	2 [304,305]	3 [307,312,313]	Very low
Isolation room	–	9 [129,131,156, 290–294,311]	7 [141,296–301]	Low	1 [314]	–	4 [306,307,312,313]	Low
Pre-emptive CP/alert code	–	–	–	Insufficient	–	–	1 [313]	Very low
Cohort patients	–	5 [156,290,292–294]	6 [130,141,299, 301–303]	Low	–	–	1 [307]	Very low
Cohort staff	–	5 [156,290–292,294]	4 [130,141,301,303]	Low	–	–	1 [306]	Very low
Environmental cleaning	1 [289]	11 [129,131,134,156, 214,290–294,311]	10 [130,295, 297–303,310]	Moderate	1 [314]	2 [304,305]	2 [306,307]	Moderate
Environmental screening	2 [289,309]	10 [129,131,134,156, 214,290–292,294,311]	10 [141,295–299, 301–303,310]	Moderate	1 [314]	2 [304,305]	4 [306,307,312,313]	Low
Antimicrobial stewardship	1 [289]	2 [214,290]	3 [130,141,297]	Moderate	–	–	3 [306,308,312]	Very low

CP, contact precautions.

TABLE 9. Quality of studies by intervention. Basic and additional measures to reduce the spread of *Stenotrophomonas maltophilia* and *Burkholderia cepacia* in hospitalized adult patients: recommended for all acute-care facilities in epidemic setting

Microorganism	*S. maltophilia* Quality of studies			Overall quality of evidence	*B. cepacia* Quality of studies			Overall quality of evidence
Intervention	Moderate	Low	Very low		Moderate	Low	Very low	
Hand hygiene	1 [315]	–	–	Moderate	–	1 [316]	2 [317,318]	Very low
Education	1 [315]	–	–	Moderate	–	1 [88]	1 [318]	Very low
Active surveillance cultures	–	–	–	Insufficient	–	–	1 [319]	Very low
Healthcare workers screening	–	–	–	Insufficient	–	–	–	Insufficient
Contact precautions	1 [315]	–	–	Moderate	–	2 [88,320]	1 [317]	Low
Isolation room	–	–	–	Insufficient	–	–	–	Insufficient
Pre-emptive CP/alert code	–	–	–	Insufficient	–	–	–	Insufficient
Cohort patients	–	–	–	Insufficient	–	1 [316]	–	Low
Cohort staff	–	–	–	Insufficient	–	–	–	Insufficient
Environmental cleaning	1 [315]	–	–	Moderate	–	1 [320]	4 [317–319,321]	Very low
Environmental screening	1 [315]	–	–	Moderate	–	3 [88,316,320]	4 [317–319,321]	Very low
Antimicrobial stewardship	–	–	–	Insufficient	–	–	–	Insufficient

CP, contact precautions.

Basic recommendations in endemic situation: ESBL-producing Enterobacteriaceae

Intervention	Evidence	Recommendation	Note
Hand hygiene (HH)	Moderate	Strong	Implement HH education programmes to reduce the transmission of ESBL+Enterobacteriaceae. HCWs should be encouraged to perform HH with an alcohol-based hand rub before and after all patient contacts. Soap and water hand washing is required when hands are visibly soiled, e.g. with body fluids or excretions. Monitoring of HH compliance and feedback to HCWs should be performed to achieve greater compliance. Detailed indications on how to monitor and improve HH compliance are provided by the WHO guidelines (level of recommendation ranked as IA–IB) (available from: http://www.who.int/gpsc/5may/tools/9789241597906/en/). The use of artificial nails should be prohibited.
Contact precautions (CP) (with the exception of *Escherichia coli*)[1]	Moderate	Strong	Implement CP for all colonized patient encounters, in all hospital settings, so as to reduce the risk of acquisition. HCWs caring for patients colonized or infected with ESBL+Enterobacteriaceae should wear gloves and gowns before entering the room and should remove

(*Continued*)

Intervention	Evidence	Recommendation	Note
			these promptly after care and then perform HH. There should be audit of adherence to CP to ensure that interventions are being correctly performed to increase the chances of success. There is no evidence available to provide recommendation on when to discontinue CP and for, or against the implementation of droplet precautions when entering the room of patients receiving CP.
Alert code (previous positive) and pre- emptive CP (with the exception of *E. coli*)[l]	Moderate	Conditional	Use alert code to identify promptly patients already known as colonized at, hospital/ward admission and perform screening and pre-emptive CP. Implement pre-emptive CP for patients admitted from ICU or other wards with cases of ESBL+Enterobacteriaceae already detected.
Isolation room (with the exception of *E. coli*)[l]	Moderate	Conditional	Isolate colonized and infected patients in a single room to reduce the risk of acquisition of ESBL+ Enterobacteriaceae. The implementation of isolation room should include monitoring for possible deleterious effects, such as clinical complications due to the reduction in contacts with doctors and nurses, decreases in the quality of life, and possible psychological adverse effects.
Education	Moderate	Conditional	Conduct educational programmes to ensure that HCWs understand why ESBL+Enterobacteriaceae are important epidemiologically, why prevention of spread is critical for control, and which measures for preventing spread have proven to be effective. Ensure regular multidisciplinary meetings to implement interventions, to review adherence audit and to report local data and feedback to all HCWs and other relevant staff.
Environmental cleaning (EC)	Moderate	Conditional	Implement regular EC procedures, which include detergents or disinfectants, depending on local practice in order to reduce the transmission rate. Ensure cleaning of patient care equipment and the environment. When available, dedicate non-critical medical items for use on individual patients colonized or infected with ESBL+Enterobacteriaceae. Shared equipment should be disinfected between use on different patients.

(*Continued*)

Intervention	Evidence	Recommendation	Note
Antimicrobial stewardship (ABS)	Moderate	Strong	Implement an ABS programme. Consider interventions that limit the use of specific antimicrobial agents based on the patients' comorbidities.
Infection prevention and control (IPC) infrastructure	NA		There is no evidence available to provide recommendations for, or against, the intervention. However, the authors suggest provision of administrative support, including economic and human resources, to prevent and control ESBL+Enterobacteriaceae transmission within the healthcare facility. Use public health resources to support the initiation of IPC interventions within hospitals. An IPC infrastructure should include environmental personnel, such as estates, domestic and janitorial representatives.

ESBL, extended-spectrum β-lactamase; HCW, healthcare worker; MDR, multidrug-resistant; NA, not available. [1]In high-risk areas such as intensive-care units (ICU), burn units and haematological units there is no evidence in favour or against the implementation of CP in patients colonized or infected with ESBL-producing *Escherichia coli*.

Basic recommendations in endemic situation: MDR-*Klebsiella pneumoniae*

Intervention	Evidence	Recommendation	Note
Hand hygiene (HH)	Moderate	Strong	Implement HH education programmes to reduce the transmission of MDR-*K. pneumoniae*. HCWs should be encouraged to perform HH with an alcohol-based hand rub before and after all patient contacts. Soap and water hand washing is required when hands are visibly soiled, e.g. with body fluids or excretions. Monitoring of HH compliance and feedback to HCWs should be performed to achieve greater compliance. Detailed indications on how to monitor and improve HH compliance are provided by the WHO guidelines (level of recommendation ranked as IA-IB) (available from: http://www.who.int/gpsc/5may/tools/9789241597906/en/). The use of artificial nails should be prohibited.
Contact precautions (CP)	Moderate	Strong	Implement CP for all colonized patient encounters, in all hospital settings, so as to reduce the risk of acquisition. HCWs caring for patients colonized or infected with MDR-*K. pneumoniae* should wear gloves and gowns before entering the room and should remove these promptly after care and then perform HH. There should be audit of adherence to CP to ensure that interventions are being correctly performed to increase the chances of success. There is no evidence available

(*Continued*)

Intervention	Evidence	Recommendation	Note
			to provide recommendation on when to discontinue CP and for, or against, the implementation of droplet precautions when entering the room of patients receiving CP.
Alert code (previous positive) and pre-emptive CP	Moderate	Conditional	Use alert code to identify promptly patients already known as colonized at hospital/ward admission and perform screening and pre-emptive CP.
Isolation room	Moderate	Strong	Isolate colonized and infected patients in a single room to reduce the risk of acquisition of MDR-*K. pneumoniae*. The implementation of isolation room should include monitoring for possible deleterious effects, such as clinical complications due to the reduction in contacts with doctors and nurses, decreases in the quality of life, and possible psychological adverse effects.
Education	Moderate	Conditional	Conduct educational programmes to ensure that HCWs understand why MDR-*K. pneumoniae* is important epidemiologically, why prevention of spread is critical for control, and which measures for preventing spread have proven to be effective. Ensure regular multidisciplinary meetings to implement interventions, to review adherence audit, to report local data and feedback to all HCWs and other relevant staff.
Environmental cleaning (EC)	Moderate	Conditional	Implement regular EC procedures, which include detergents or disinfectants, depending on local practice to reduce the transmission rate. Ensure cleaning of patient care equipment and the environment. When available, dedicate non-critical medical items for use on individual patients colonized or infected with MDR-*K. pneumoniae*. Shared equipment should be disinfected between use on different patients.
Antimicrobial stewardship (ABS)	Moderate	Conditional	Implement an ABS programme. Consider interventions that limit the use of specific antimicrobial agents based on patients' case-mix.
Infection prevention and control (IPC) infrastructure	NA		There is no evidence available to provide recommendations for, or against, the intervention. However, the authors suggest provision of administrative support, including economic and human resources, to prevent and control MDR-*K. pneumoniae* transmission within the healthcare facility. Use public health resources to support the initiation of IPC interventions within hospitals. An IPC infrastructure should include

(*Continued*)

Intervention	Evidence	Recommendation	Note
			environmental personnel, such as estates, domestic and janitorial representatives.

HCW, healthcare worker; MDR, multidrug-resistant; NA, not available.

Basic recommendations in endemic situation: MDR-*Pseudomonas aeruginosa*

Intervention	Evidence	Recommendation	Note
Hand hygiene (HH)	Moderate	Strong	Implement HH education programmes to reduce the transmission of MDR-*P. aeruginosa*. HCWs should be encouraged to perform HH with an alcohol-based hand rub before and after all patient contacts. Soap and water hand washing is required when hands are visibly soiled, e.g. with body fluids or excretions. Monitoring of HH compliance and feedback to HCWs should be performed to achieve greater compliance. Detailed indications on how to monitor and improve HH compliance are provided by the WHO guidelines (level of recommendation ranked as IA-IB) (available from: http://www.who.int/gpsc/5may/tools/9789241597906/en/). The use of artificial nails should be prohibited.
Contact precautions (CP)	Moderate	Strong	Implement CP for all colonized patient encounters, in all hospital settings, so as to reduce the risk of acquisition. HCWs caring for patients colonized or infected with MDR-*P. aeruginosa* should wear gloves and gowns before entering the room and should remove these, promptly after care and then perform HH. There should be audit of adherence to CP to ensure that interventions are being correctly performed to increase the chances of success. There is no evidence available to provide recommendations on when to discontinue CP and for, or against, the implementation of droplet precautions when entering the room of patients receiving CP.
Alert code (previous positive) and pre-emptive CP	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Isolation room	NA	Conditional	Regardless of the availability of evidence specifically related to *P. aeruginosa*, the authors of these guidelines believed that there was sufficient evidence for the value of an isolation room as demonstrated for other microorganisms, including other MDR microorganisms,

(*Continued*)

Intervention	Evidence	Recommendation	Note
			to also recommend this approach here until studies show otherwise.
Education	Moderate	Conditional	Conduct educational programmes to ensure that HCWs understand why *P. aeruginosa* is important epidemiologically, why prevention of spread is critical for control, and which measures for preventing spread have proven to be effective. Ensure regular multidisciplinary meetings to implement interventions, to review adherence audit, to report local data and feedback to all HCWs and other relevant staff.
Environmental cleaning (EC)	Moderate	Conditional	Implement regular EC procedures, which include detergents or disinfectants, depending on local practice to reduce the transmission rate. Ensure cleaning of patient care equipment and the environment. When available, dedicate non-critical medical items for use on individual patients colonized or infected with MDR-*P. aeruginosa*. Shared equipment should be disinfected between use on different patients.
Antimicrobial stewardship (ABS)	Moderate	Conditional	Implement an ABS programme. Consider interventions that limit the use of specific antimicrobial agents based on patients' case-mix.
Infection prevention and control (IPC) infrastructure	NA		There is no evidence available to provide recommendations for, or against, the intervention. However, the authors suggest provision of administrative support, including economic and human resources, to prevent and control MDR-*P. aeruginosa* transmission within the healthcare facility. Use public health resources to support the initiation of IPC interventions within hospitals. An IPC infrastructure should include environmental personnel such as estates, domestic and janitorial representatives.

HCW, healthcare worker; MDR, multidrug-resistant; NA, not available.

Basic recommendations in endemic situation: MDR-*Acinetobacter baumannii*

Intervention	Evidence	Recommendation	Note
Hand hygiene (HH)	Moderate	Strong	Implement HH education programmes to reduce the transmission of MDR-*A. baumannii*. HCWs should be encouraged to perform HH with an alcohol-based hand rub before and after all patient contacts. Soap and water hand washing is required when hands are visibly soiled, e.g. with body fluids or excretions. Monitoring of

(*Continued*)

Intervention	Evidence	Recommendation	Note
			HH compliance and feedback to HCWs should be performed to achieve greater compliance. Detailed indications on how to monitor and improve HH compliance are provided by the WHO guidelines (level of recommendation ranked as IA-IB) (available from: http://www.who.int/gpsc/5may/tools/9789241597906/en/). The use of artificial nails should be prohibited.
Contact precautions (CP)	Moderate	Strong	Implement CP for all colonized patient encounters, in all hospital settings, so as to reduce the risk of acquisition. HCWs caring for patients colonized or infected with MDR-*A. baumannii* should wear gloves and gowns before entering the room and should remove these promptly after care and then perform HH. There should be audit of adherence to CP to ensure that interventions are being correctly performed to increase the chances of success. There is no evidence available to provide recommendations on when to discontinue CP and for, or against, the implementation of the usage of droplet precautions when entering the room of patients receiving CP.
Alert code (previous positive) and pre-emptive CP	Moderate	Strong	Use alert code to identify promptly patients already known as colonized at hospital/ward admission and perform screening and pre-emptive CP.
Isolation room	Moderate	Strong	Isolate colonized and infected patients in a single room to reduce the risk of acquisition of MDR-*A. baumannii*. The implementation of isolation room should include monitoring for possible deleterious effects such as clinical complications due to the reduction in contacts with doctors and nurses, decreases in the quality of life, and possible psychological adverse effects.
Education	Moderate	Strong	Conduct educational programmes to ensure that HCWs understand why MDR-*A. baumannii* is important epidemiologically, why prevention of spread is critical for control, and which measures for preventing spread have proven to be effective. Ensure regular multidisciplinary meetings to implement interventions, to review adherence audit and to report local data and feedback to all HCWs and other relevant staff.
Environmental cleaning (EC)	Moderate	Strong	Implement regular EC procedures, which include detergents or disinfectants, depending on local practice to reduce the transmission rate. Ensure cleaning of patient care equipment and the environment. When available, dedicate non-critical medical items for use on

(*Continued*)

Intervention	Evidence	Recommendation	Note
			individual patients colonized or infected with MDR-*A. baumannii*. Shared equipment should be disinfected between use on different patients.
Antimicrobial stewardship (ABS)	Moderate	Conditional	Implement an ABS programme. Consider interventions that limit the use of specific antimicrobial agents based on patients' case-mix.
Infection prevention and control (IPC) infrastructure	NA		There is no evidence available to provide recommendations for or against the intervention. However, the authors suggest provision of administrative support, including economic and human resources, to prevent and control MDR-*A. baumannii* transmission within the healthcare facility. Use public health resources to support the initiation of IPC interventions within hospitals. An IPC infrastructure should include environmental personnel, such as estates, domestic and janitorial representatives.

HCW, healthcare worker; MDR, multidrug-resistant; NA, not available.

Basic recommendations in endemic situation: *Burkholderia cepacia*

There is no evidence available to provide recommendations for, or against, any intervention. However, regardless of the availability of evidence specifically related to *B. cepacia*, the authors of these guidelines believed that there was sufficient evidence for the value of effective HH as demonstrated for other microorganisms, including other MDR microorganisms, to also recommend this approach here until studies show otherwise.

Basic recommendations in endemic situation: *Stenotrophomonas maltophilia*

Intervention	Evidence	Recommendation	Note
Hand hygiene (HH)	Insufficient	Strong	Regardless of the availability of evidence specifically related to *S. maltophilia*, the authors of these guidelines believed that there was sufficient evidence for the value of effective HH as demonstrated for other microorganisms, including other MDR microorganisms, to also recommend this approach here until studies show otherwise. Implement HH education programmes to reduce the transmission of *S. maltophilia*. HCWs should be encouraged to perform HH with an alcohol-based hand rub before and after all patient contacts. Soap and water hand washing is required when hands are visibly soiled, e.g. with body fluids or excretions. Monitoring of HH compliance and feedback to HCWs should be performed to achieve greater compliance. Detailed indications on how to monitor and improve HH compliance are provided by the WHO guidelines (level of recommendation ranked as IA-IB) (available from: http://www.

(*Continued*)

Intervention	Evidence	Recommendation	Note
			who.int/gpsc/5may/tools/9789241597906/en/). The use of artificial nails should be prohibited.
Contact precautions (CP)	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Isolation room	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Alert code (previous positive) and pre-emptive CP	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Education	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Environmental cleaning (EC)	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Antimicrobial stewardship (ABS)	Low	Conditional	Implement an ABS programme. Consider interventions that limit the use of specific antimicrobial agents based on patients' case-mix.
Infection prevention and control (IPC) infrastructure	NA		There is no evidence available to provide recommendations for, or against, the intervention. However, the authors suggest provision of administrative support, including economic and human resources, to prevent and control *S. maltophilia* transmission within the healthcare facility. Use public health resources to support the initiation and support for IPC interventions within hospitals. An IPC infrastructure should include environmental personnel, such as estates, domestic and janitorial representatives.

NA, not available.

Basic and additional specific approaches in outbreak situation: ESBL-producing Enterobacteriaceae

Intervention	Evidence	Recommendation	Note
Hand hygiene (HH)	Moderate	Strong	Implement HH education programmes to reduce the transmission of ESBL+Enterobacteriaceae. HCWs should be encouraged to perform HH with an alcohol-based hand rub before and after all patient contacts. Soap and water hand washing is required when hands are visibly soiled, e.g. with body fluids or excretions. Monitoring of HH compliance and feedback to HCWs should be performed to achieve greater compliance. Detailed indications on how to monitor and improve HH compliance are provided by the WHO guidelines (level of recommendation ranked as IA-IB) (available from: http://www.who.int/gpsc/5may/tools/9789241597906/en/). The use of artificial nails should be prohibited.

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Intervention	Evidence	Recommendation	Note
Active screening cultures (ASC)	Moderate	Strong	Implement a programme of ASC at hospital admission followed by CP to reduce the rate of colonization with ESBL+Enterobacteriaceae. Screening cultures should use stool samples or swab samples from the rectum or perirectal area as well as samples from the inguinal area and manipulated sites, e.g. catheters and areas of broken skin such as wounds. The frequency of screening cultures should be based on the local prevalence of the microorganism, patient colonization risk, and the case mix of the unit. Consider performing ASC at the time of hospital admission for high-risk patients or for all patients in high-risk units such as cancer or ICU wards, according to local incidence or prevalence data. Admission, discharge and weekly patient screening might also be considered to provide feedback to HCWs and to assess the effectiveness of interventions. Periodic (e.g. weekly) ASC might be performed for patients remaining in the hospital at high risk for carriage of MDR-GNB because of ward type (ICU), prolonged antibiotic(s) therapy, underlying disease, long duration of stay, presence of devices and surgery. Before transferring patients with ESBL+Enterobacteriaceae to other healthcare facilities (acute and non-acute care) ensure communication of ESBL+Enterobacteriaceae status.
Contact precautions (CP)	Moderate	Strong	Implement CP for all colonized patient encounters, in all hospital settings, so as to reduce the risk of acquisition. HCWs caring for patients colonized or infected with ESBL+Enterobacteriaceae should wear gloves and gowns before entering the room and should remove these promptly after care and then perform HH. There should be audit of adherence to CP to ensure that interventions are being correctly performed to increase the chances of success. Evidence for when to discontinue CP, in patients colonized with ESBL+Enterobacteriaceae, is heterogeneous and derives from two interventions implementing CP during all hospitalization or until two negative cultures are obtained. There is no evidence available to provide recommendations for, or against, the implementation of droplet precautions to enter the room of patients in CP.
Alert code (previous positive) and pre-emptive CP	Moderate	Strong	Use alert code to identify promptly patients already known as colonized at hospital/ward admission and perform screening and pre-emptive CP. Implement pre-emptive CP for patients admitted from ICU or wards with cases of ESBL+Enterobacteriaceae already detected.
Cohort patients	Moderate	Conditional	Cohort patients with the same ESBL+Enterobacteriaceae in designated areas.

(*Continued*)

Intervention	Evidence	Recommendation	Note
Cohort staff	Moderate	Conditional	Cohort staff to reduce the risk of acquisition of ESBL+Enterobacteriaceae.
Isolation room	Moderate	Strong	Isolate colonized and infected patients in a single room to reduce the risk of acquisition. The implementation of isolation room should include monitoring for possible deleterious adverse effects such as clinical complications due to the reduction in contacts with doctors and nurses, decreases in the quality of life, and possible psychological adverse effects.
Education	Moderate	Strong	Conduct educational programmes to ensure that HCWs understand why ESBL+Enterobacteriaceae are important epidemiologically, why prevention of spread is critical for control, and which measures for preventing spread have proven to be effective. Ensure regular multidisciplinary meetings to implement interventions, to review adherence audit, to report local data and feedback to all HCWs and other relevant staff.
Environmental cleaning (EC)	Moderate	Strong	Monitor cleaning performance to ensure consistent EC. Vacate units for intensive cleaning. Review use of disinfectant agents, methods and meticulousness of cleaning, dilutions and contact time of the hospital cleaning procedures. Implement EC procedures with audit and feedback to reduce transmission of ESBL+Enterobacteriaceae. Specify in protocols which items are to be disinfected, which disinfectant to use, and how often items need to be disinfected. Dedicate the use of non-critical patient-care equipment to a single patient or cohort of patients infected or colonized with ESBL+Enterobacteriaceae. Specific protocols for the disinfection of endoscopes and respiratory equipment should be implemented locally. Consider closure of the ward or the unit to new admissions in order also to facilitate cleaning until there is evidence of control of transmission.
Environmental screening	Moderate	Conditional	Perform environmental sampling from surfaces (mattresses, beds, bedside tables, tables, chairs, armchairs, washbasins, window sills) that had been in contact with patients colonized or infected by ESBL+Enterobacteriaceae.
Antimicrobial stewardship (ABS)	Moderate	Strong	Plan interventions of restriction of antibiotic usage to reduce the spread of ESBL+Enterobacteriaceae.
Healthcare-workers (HCWs) screening	Low	Conditional	Screen HCWs for ESBL+Enterobacteriaceae if they are epidemiologically linked to a cluster of cases.
Chlorhexidine gluconate for patient bathing	NA		There is no evidence available to provide recommendations for, or against, the intervention.

(*Continued*)

Intervention	Evidence	Recommendation	Note
Infection prevention and control (IPC) infrastructure	Moderate	Conditional	Provide administrative support, including economic and human resources, to prevent and control ESBL+Enterobacteriaceae outbreak transmission.

ESBL, extended-spectrum β-lactamase; HCW, healthcare worker; MDR, multidrug-resistant; NA, not available.

Basic and additional specific approaches in outbreak situation: MDR-*Klebsiella pneumoniae*

Intervention	Evidence	Recommendation	Note
Hand hygiene (HH)	Very low	Strong	Regardless of the availability of very low level of evidence specifically related to *K. pneumoniae*, the authors of these guidelines believed that there was sufficient evidence for the value of effective HH as demonstrated for other microorganisms, including other MDR microorganisms, to also recommend this approach here until studies show otherwise. Implement HH education programmes to reduce the transmission of MDR-*K. pneumoniae*. HCWs should be encouraged to perform HH with an alcohol-based hand rub before and after all patient contacts. Soap and water hand washing is required when hands are visibly soiled, e.g. with body fluids or excretions. Monitoring of HH compliance and feedback to HCWs should be performed to achieve greater compliance. Detailed indications on how to monitor and improve HH compliance are provided by the WHO guidelines (level of recommendation ranked as IA-IB) (available from: http://www.who.int/gpsc/5may/tools/9789241597906/en/). The use of artificial nails should be prohibited.
Active screening cultures (ASC)	Moderate	Strong	Implement a programme of ASC at hospital admission followed by CP to reduce the rate of colonization with MDR-*K. pneumoniae*. Screening cultures should use stool samples or swab samples from the rectum or perirectal area as well as samples from the inguinal area and manipulated sites, e.g. catheters and areas of broken skin such as wounds. The frequency of screening cultures should be based on the local prevalence of the microorganism, patient colonization risk, and the case mix of the unit. Consider performing ASC at the time of hospital admission for high-risk patients or for all patients in high-risk units such as cancer or ICU wards, according to local incidence or prevalence data. Admission, discharge and weekly patient screening might also be considered to provide feedback to HCWs and to assess the effectiveness of interventions. Periodic (e.g.weekly) ASC might be performed for patients remaining in the hospital at high risk for carriage of MDR-GNB because of ward type (ICU), prolonged antibiotic(s) therapy, underlying disease, long duration of stay, presence of devices and surgery. Before transferring patients with

(*Continued*)

Intervention	Evidence	Recommendation	Note
			MDR-*K. pneumoniae* to other healthcare facilities (acute and non-acute care) ensure communication of MDR-*K. pneumoniae* status.
Contact precautions (CP)	Moderate	Strong	Implement CP for all colonized patient encounters, in all hospital settings, so as to reduce the risk of acquisition. HCWs caring for patients colonized or infected with MDR-*K. pneumoniae* should wear gloves and gowns before entering the room and should remove these promptly after care and then perform HH. There should be audit of adherence to CP to ensure that interventions are being correctly performed to increase the chances of success. Evidence of when to discontinue CP is available only from one intervention where CP were maintained for the entire duration of hospitalization. There is no evidence available to provide recommendations for, or against, the usage of droplet precautions to enter the room of patients in CP.
Alert code (previous positive) and pre-emptive CP	Moderate	Strong	Use alert code to identify promptly patients already known as colonized at hospital/ward admission and perform screening and pre-emptive CP.
Cohort patients	Moderate	Conditional	Cohort patients with the same MDR-*K. pneumoniae* in designated areas.
Cohort staff	Moderate	Strong	Cohort staff to reduce the risk of acquisition of MDR-*K. pneumoniae*.
Isolation room	Moderate	Strong	Isolate colonized and infected patients in a single room to reduce the risk of acquisition. The implementation of isolation room should include monitoring for possible adverse effects such as clinical complications due to the reduction of contacts with doctors and nurses, decreases in the quality of life, and possible psychological adverse effects.
Education	Moderate	Conditional	Conduct educational programmes to ensure that HCWs understand why MDR-*K. pneumoniae* is important epidemiologically, why prevention of spread is critical for control, and which measures for preventing spread have proven to be effective. Ensure regular multidisciplinary meetings to implement interventions, to review adherence audit, to report local data and feedback to all HCWs and other relevant staff.
Environmental cleaning (EC)	Moderate	Conditional	Monitor cleaning performance to ensure consistent EC. Vacate units for intensive cleaning. Review use of disinfectant agents, methods and meticulousness of cleaning, dilutions, and contact time of the hospital cleaning procedures. Implement EC procedures with audit and feedback to reduce transmission of MDR-*K. pneumoniae*. Specify in protocols which items are to be disinfected, which disinfectant to use, and how often items need to be disinfected. Dedicate the use of non-critical patient-care equipment to a single

(*Continued*)

Intervention	Evidence	Recommendation	Note
			patient or cohort of patients infected or colonized with MDR-*K. pneumoniae*. Specific protocols for the disinfection of endoscopes and respiratory equipment should be implemented locally. Consider closure of the ward or the unit to new admissions in order also to facilitate cleaning until there is evidence of control of transmission.
Environmental screening	Low	Conditional	Perform environmental sampling and UV light surveillance of surfaces (mattresses, beds, bedside tables, tables, chairs, armchairs, washbasins, window sills) that have been in contact with patients colonized or infected by MDR-*K. pneumoniae*.
Antimicrobial stewardship (ABS)	Very low	Conditional	Plan interventions of restriction of antibiotic usage to reduce the spread of MDR-*K. pneumoniae*.
Healthcare-workers (HCWs) screening	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Chlorhexidine gluconate for patient bathing	Low	Conditional	Bathing patients with chlorhexidine soap or chlorhexidine-impregnated cloths may be useful as a part of a multifaceted approach to reduce transmission of MDR-*K. pneumoniae*.
Infection prevention and control (IPC) infrastructure	Moderate	Conditional	Provide administrative support, including economic and human resources, to prevent and control MDR-*K. pneumoniae* outbreak transmission.

HCW, healthcare worker; MDR, multidrug-resistant; NA: not available.

Basic and additional specific approaches in outbreak situation: MDR-*Pseudomonas aeruginosa*

Intervention	Evidence	Recommendation	Note
Hand hygiene (HH)	Very low	Strong	Regardless of the availability of a very low level of evidence specifically related to *P. aeruginosa*, the authors of these guidelines believed that there was sufficient evidence for the value of effective HH as demonstrated for other microorganisms, including other MDR microorganisms, to also recommend this approach here until studies show otherwise. Implement HH education programmes to reduce the transmission of *P. aeruginosa*. HCWs should be encouraged to perform HH with an alcohol-based hand rub before and after all patient contacts. Soap and water hand washing is required when hands are visibly soiled, e.g. with body fluids or excretions. Monitoring of HH compliance and feedback to HCWs should be performed to achieve greater compliance. Detailed indications on how to monitor and improve HH compliance are provided by the WHO guidelines (level of recommendation ranked as IA-IB) (available from: http://www.who.int/gpsc/5may/tools/9789241597906/en/). The use of artificial nails should be prohibited.

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Intervention	Evidence	Recommendation	Note
Active screening cultures (ASC)	Very low	Strong	Implement a programme of ASC at hospital admission followed by CP to reduce the rate of colonization with MDR-*P. aeruginosa*. Regardless of the availability of a very low level of evidence specifically related to *P. aeruginosa*, the authors of these guidelines believed that there was sufficient evidence for the value of effective ASC as demonstrated for other microorganisms, including other MDR microorganisms, to also recommend this approach here until studies show otherwise. Screening cultures should use stool samples or swab samples from the rectum or perirectal area as well as samples from the inguinal area and manipulated sites, e.g. catheters and areas of broken skin such as wounds. The frequency of screening cultures should be based on the local prevalence of the microorganism, patient colonization risk, and the case mix of the unit. Consider performing ASC at the time of hospital admission for high-risk patients or for all patients in high-risk units such as cancer or ICU wards, according to local incidence or prevalence data. Admission, discharge and weekly patient screening might also be considered to provide feedback to HCWs and to assess the effectiveness of interventions. Periodic (e.g. weekly) ASC might be performed for patients remaining in the hospital at high risk for carriage of MDR-*P. aeruginosa* because of ward type (ICU), prolonged antibiotic(s) therapy, underlying disease, long duration of stay, presence of devices and surgery. Before transferring patients with MDR-*P. aeruginosa* to other healthcare facilities (acute and non-acute care) ensure communication of MDR-*P. aeruginosa* status.
Contact precautions (CP)	Very low	Strong	Implement CP for all colonized patient encounters, in all hospital settings, so as to reduce the risk of acquisition. HCWs caring for patients colonized or infected with MDR-*P. aeruginosa* should wear gloves and gowns before entering the room and should remove these promptly after care and then perform HH. There should be audit of adherence to CP to ensure that interventions are being correctly performed to increase the chances of success. Regardless of the availability of a very low level of evidence specifically related to *P. aeruginosa*, the authors of these guidelines believed that there was sufficient evidence for the value of CP as demonstrated for other microorganisms, including other MDR microorganisms, to also recommend this approach here until studies show otherwise. There is no evidence available to provide recommendations on when to discontinue CP and for, or against, the implementation of the usage of droplet precautions to enter the room of patients in CP.

(*Continued*)

Intervention	Evidence	Recommendation	Note
Alert code (previous positive) and pre-emptive CP	Very low	Conditional	Use alert code to identify promptly patients already known as colonized at hospital/ward admission and perform screening and pre-emptive CP.
Cohort patients	Very low	Conditional	Cohort patients with the same MDR-*P. aeruginosa* in designated areas.
Cohort staff	Very low	Conditional	Cohort staff to reduce the risk of acquisition of MDR-*P. aeruginosa*.
Isolation room	Low	Strong	Isolate colonized and infected patients in a single room to reduce the risk of acquisition. The implementation of isolation room should include monitoring for possible adverse effects such as clinical complications due to the reduction in contacts with doctors and nurses, decreases in the quality of life, and possible psychological adverse effects.
Education	Very low	Conditional	Conduct educational programmes to ensure that HCWs understand why MDR-*P. aeruginosa* is important epidemiologically, why prevention of spread is critical for control, and which measures for preventing spread have proven to be effective. Ensure regular multidisciplinary meetings to implement interventions, to review adherence audit, to report local data and feedback to all HCWs and other relevant staff.
Environmental cleaning (EC)	Moderate	Conditional	Monitor cleaning performance to ensure consistent EC. Vacate units for intensive cleaning. Review use of disinfectant agents, methods and meticulousness of cleaning, dilutions and contact time of the hospital cleaning procedures. Implement EC procedures with audit and feedback to reduce transmission of MDR-*P. aeruginosa*. Specify in protocols which items are to be disinfected, which disinfectant to use, and how often items need to be disinfected. Dedicate the use of non-critical patient-care equipment to a single patient or cohort of patients infected or colonized with MDR-*P. aeruginosa*. Specific protocols for the disinfection of endoscopes and respiratory equipment should be implemented locally. Consider closure of the ward or the unit to new admissions in order also to facilitate cleaning until there is evidence of control of transmission.
Environmental screening	Low	Conditional	Perform environmental samples from surfaces (mattresses, beds, bedside tables, tables, chairs, armchairs, washbasins, window sills) that have been in contact with patients colonized or infected by MDR-*P. aeruginosa*.
Antimicrobial stewardship (ABS)	Very low	Conditional	Plan interventions of restriction of antibiotic usage to reduce the spread of MDR-*P. aeruginosa*.
Healthcare-workers (HCWs) screening	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Chlorhexidine gluconate for patient bathing	NA		There is no evidence available to provide recommendations for, or against, the intervention.

(*Continued*)

Intervention	Evidence	Recommendation	Note
Infection prevention and control (IPC) infrastructure	NA		There is no evidence available to provide recommendations for, or against, the intervention. However, authors suggest provision of administrative support, including economic and human resources, to prevent and control MDR-*P. aeruginosa* outbreak transmission.

HCW, healthcare worker; MDR, multidrug-resistant; NA: not available.

Basic and additional specific approaches in outbreak situation: MDR-*Acinetobacter baumannii*

Intervention	Evidence	Recommendation	Note
Hand hygiene (HH)	Moderate	Strong	Implement HH education programmes to reduce the transmission of MDR-*A. baumannii*. HCWs should be encouraged to perform HH withan alcohol-based hand rub before and after all patient contacts. Soap and water hand washing is required when hands are visibly soiled, e.g. with body fluids or excretions. Monitoring of HH compliance and feedback to HCWs should be performed to achieve greater compliance. Detailed indications on how to monitor and improve HH compliance are provided by the WHO guidelines (level of recommendation ranked as IA-IB) (available from: http://www.who.int/gpsc/5may/tools/9789241597906/en/). The use of artificial nails should be prohibited.
Active screening cultures (ASC)	Moderate	Strong	Implement a programme of ASC at hospital admission followed by CP to reduce the rate of colonization with MDR-*A. baumannii*. Screening cultures should use stool samples or swab samples from the rectum or perirectal area as well as samples from the inguinal area and manipulated sites, e.g. catheters and areas of broken skin such as wounds. The frequency of screening cultures should be based on the local prevalence of the microorganism, patient colonization risk, and the case mix of the unit. Consider performing ASC at the time of hospital admission for high-risk patients or for all patients in high-risk units such as cancer or ICU wards, according to local incidence or prevalence data. Admission, discharge and weekly patient screening might also be considered to provide feedback to HCWs and to assess the effectiveness of interventions. Periodic (e.g. weekly) ASC might be performed for patients remaining in the hospital at high risk for carriage of MDR-*A. baumannii* because of ward type (ICU), prolonged antibiotic(s) therapy, underlying disease, long duration of stay, presence of devices and surgery. Before transferring patients with MDR-*A. baumannii* to other healthcare facilities (acute and non-acute care) ensure communication of MDR-*A. baumannii* status.
Contact precautions (CP)	Moderate	Strong	Implement CP for all colonized patient encounters, in all hospital settings, so as to reduce the risk of acquisition. HCWs caring for

(*Continued*)

Intervention	Evidence	Recommendation	Note
			patients colonized or infected with MDR-*A. baumannii* should wear gloves and gowns before entering the room and should remove these promptly after care and then perform HH. There should be audit of adherence to CP to ensure that interventions are being correctly performed to increase the chances of success. Evidence of when to discontinue CP is very heterogeneous (ranging from keeping CP throughout the hospitalization, to discontinuing it after two or three negative cultures) and does not allow provision of any specific recommendation. Consider using droplet precautions to enter the room of colonized or infected patients in ICU settings and for all aereosol-producing procedures (low level of evidence; conditional recommendation).
Alert code (previous positive) and pre-emptive CP	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Cohort patients	Very low	Conditional	Cohort patients with the same MDR-*A. baumannii* in designated areas.
Cohort staff	Low	Conditional	Cohort staff to reduce the risk of acquisition of MDR-*A. baumannii*.
Isolation room	Low	Strong	Isolate colonized and infected patients in a single room to reduce the risk of acquisition. The implementation of isolation room should include monitoring for possible adverse effects such as clinical complications due to the reduction in contacts with doctors and nurses, decreases of the quality of life, and possible psychological adverse effects.
Education	Moderate	Conditional	Conduct educational programmes to ensure that HCWs understand why MDR-*A. baumannii* is important epidemiologically, why prevention of spread is critical for control, and which measures for preventing spread have proven to be effective. Ensure regular multidisciplinary meetings to implement interventions, to review adherence audit and to report local data and feedback to all HCWs and other relevant staff.
Environmental cleaning (EC)	Moderate	Strong	Monitor cleaning performance to ensure consistent EC. Vacate units for intensive cleaning. Review use of disinfectant agents, methods and meticulousness of cleaning, dilutions and contact time of the hospital cleaning procedures. Implement EC procedures with audit and feedback to reduce transmission of MDR-*A. baumannii*. Specify in protocols which items are to be disinfected, which disinfectant to use, and how often items need to be disinfected. Dedicate the use of non-critical patient-care equipment to a single patient or cohort of patients infected or colonized with MDR-*A. baumannii*. Specific protocols for the disinfection of endoscopes and respiratory equipment should be implemented locally. Consider closure of the ward or the unit to

(*Continued*)

Intervention	Evidence	Recommendation	Note
			new admissions in order also to facilitate cleaning until there is evidence of control of transmission.
Environmental screening	Moderate	Conditional	Perform environmental sampling from surfaces (mattresses, beds, bedside tables, tables, chairs, armchairs, washbasins, window sills) that have been in contact with patients colonized or infected by MDR-*A. baumannii*.
Antimicrobial stewardship (ABS)	Moderate	Conditional	Plan interventions of restriction of antibiotic usage to reduce the spread of MDR-*A. baumannii*.
Healthcare-workers (HCWs) screening	Very low	Conditional	Screen HCWs for MDR-*A. baumannii* if they are epidemiologically linked to a cluster of cases.
Chlorhexidine gluconate for patient bathing	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Infection prevention and control (IPC) infrastructure	Very low	Conditional	Provide administrative support, including economic and human resources, to prevent and control MDR-*A. baumannii* outbreak transmission.

Basic and additional specific approaches in outbreak situation: *Burkholderia cepacia*

Intervention	Evidence	Recommendation	Note
Hand hygiene (HH)	Very low	Strong	Regardless of the availability of very low level of evidence specifically related to *B. cepacia*, the authors of these guidelines believed that there was sufficient evidence for the value of effective HH as demonstrated for other microorganisms, including other MDR microorganisms, to also recommend this approach here until studies show otherwise. Implement HH education programmes to reduce the transmission of *B. cepacia*. HCWs should be encouraged to perform HH with an alcohol-based hand rub before and after all patient contacts. Soap and water hand washing is required when hands are visibly soiled, e.g. with body fluids or excretions. Monitoring of HH compliance and feedback to HCWs should be performed to achieve greater compliance. Detailed indications on how to monitor and improve HH compliance are provided by the WHO guidelines (level of recommendation ranked as IA-IB) (available from: http://www.who.int/gpsc/5may/tools/9789241597906/en/). The use of artificial nails should be prohibited.
Active screening cultures (ASC)	Very low	Conditional	Implement a programme of ASC at hospital admission followed by CP to reduce the rate of colonization with *B. cepacia*. Screening cultures should use stool samples or swab samples from the rectum or perirectal area as well as samples from the inguinal area and manipulated sites, e.g. catheters and areas of broken skin such

(*Continued*)

Intervention	Evidence	Recommendation	Note
			as wounds. The frequency of screening cultures should be based on the local prevalence of the microorganism, patient colonization risk, and the case mix of the unit. Consider performing ASC at the time of hospital admission for high-risk patients or for all patients in high-risk units such as cancer or ICU wards, according to local incidence or prevalence data. Admission, discharge and weekly patient screening might also be considered to provide feedback to HCWs and to assess the effectiveness of interventions. Periodic (e.g. weekly) ASC might be performed for patients remaining in the hospital at high risk for carriage of MDR-GNB because of ward type (ICU), prolonged antibiotic(s) therapy, underlying disease, long duration of stay, presence of devices and surgery. Before transferring patients with *B. cepacia* to other healthcare facilities (acute and non-acute care) ensure communication of *B. cepacia* status.
Contact precautions (CP)	Low	Conditional	Implement CP for all colonized patient encounters, in all hospital settings, so as to reduce the risk of acquisition. HCWs caring for patients colonized or infected with *B. cepacia* should wear gloves and gowns before entering the room and should remove these promptly after care and then perform HH. There should be audit of adherence to CP to ensure that interventions are being correctly performed to increase the chances of success. There is no evidence available to provide recommendations on when to discontinue CP and for, or against, the implementation of the usage of droplet precautions to enter the room of patients in CP.
Alert code (previous positive) and pre-emptive CP	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Cohort patients	Low	Conditional	Cohort patients with *B. cepacia* in designated areas.
Cohort staff	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Isolation room	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Education	Very low	Conditional	Conduct educational programmes to ensure that HCWs understand why *B. cepacia* is important epidemiologically, why prevention of spread is critical for control, and which measures for preventing spread have proven to be effective. Ensure regular multidisciplinary meetings to implement interventions, to review adherence audit, to report local data and feedback to all HCWs and other relevant staff.
Environmental cleaning (EC)	Very low	Conditional	Monitor cleaning performance to ensure consistent EC. Vacate units for intensive cleaning. Review use of disinfectant agents, methods and meticulousness of cleaning, dilutions and contact

(*Continued*)

Intervention	Evidence	Recommendation	Note
			time of the hospital cleaning procedures. Implement EC procedures with audit and feedback to reduce transmission of *B. cepacia*. Specify in protocols which items are to be disinfected, which disinfectant to use, and how often items need to be disinfected. Dedicate the use of non-critical patient-care equipment to a single patient or cohort of patients infected or colonized with *B. cepacia*. Specific protocols for the disinfection of endoscopes and respiratory equipment should be implemented locally. Consider closure of the ward or the unit to new admissions in order also to facilitate cleaning until there is evidence of control of transmission.
Environmental screening	Very low	Conditional	Perform environmental sampling from surfaces (mattresses, beds, bedside tables, tables, chairs, armchairs, washbasins, window sills) that have been in contact with patients colonized or infected by *B. cepacia*.
Antimicrobial stewardship (ABS)	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Healthcare-workers (HCWs) screening	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Chlorhexidine gluconate for patient bathing	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Infection prevention and control (IPC) infrastructure	NA		There is no evidence available to provide recommendations for, or against, the intervention. However, authors suggest provision of administrative support, including economic and human resources, to prevent and control *B. cepacia* outbreak transmission.

Basic and additional specific approaches in outbreak situation: *Stenotrophomonas maltophilia*

Intervention	Evidence	Recommendation	Note
Hand hygiene (HH)	Moderate	Strong	Implement HH education programmes to reduce the transmission of *S. maltophilia*. HCWs should be encouraged to perform HH with an alcohol-based hand rub before and after all patient contacts. Soap and water hand washing is required when hands are visibly soiled, e.g. with body fluids or excretions. Monitoring of HH compliance and feedback to HCWs should be performed to achieve greater compliance. Detailed indications on how to monitor and improve HH compliance are provided by the WHO guidelines (level of recommendation ranked as IA-IB) (available from: http://www.who.int/gpsc/5may/tools/9789241597906/en/). The use of artificial nails should be prohibited.

(*Continued*)

Intervention	Evidence	Recommendation	Note
Active screening cultures (ASC)	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Contact precautions (CP)	Moderate	Conditional	Implement CP for all colonized patient encounters, in all hospital settings, so as to reduce the risk of acquisition. HCWs caring for patients colonized or infected with *S. maltophilia* should wear gloves and gowns before entering the room and should remove these promptly after care and then perform HH. There should be audit of adherence to CP to ensure that interventions are being correctly performed to increase the chances of success. There is no evidence available to provide recommendations on when to discontinue CP and for, or against, the implementation of the usage of droplet precautions to enter the room of patients in CP.
Alert code (previous positive) and pre-emptive CP	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Cohort patients	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Cohort staff	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Isolation room	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Education	Moderate	Conditional	Conduct educational programmes to ensure that HCWs understand why *S. maltophilia* is important epidemiologically, why prevention of spread is critical for control, and which measures for preventing spread have proven to be effective. Ensure regular multidisciplinary meetings to implement interventions, to review adherence audit, to report local data and feedback to all HCWs and other relevant staff.
Environmental cleaning (EC)	Moderate	Conditional	Monitor cleaning performance to ensure consistent EC. Vacate units for intensive cleaning. Review use of disinfectant agents, methods and meticulousness of cleaning, dilutions and contact time of the hospital cleaning procedures. Implement EC procedures with audit and feedback to reduce transmission of *S. malthopilia*. Specify in protocols which items are to be disinfected, which disinfectant to use, and how often items need to be disinfected. Dedicate the use of non-critical patient-care equipment to a single patient or cohort of patients infected or colonized with *S. maltophilia*. Specific protocols for the disinfection of endoscopes and respiratory equipment should be implemented locally. Consider closure of the ward or the unit to new admissions in order also to facilitate cleaning until there is evidence of control of transmission.

(*Continued*)

Intervention	Evidence	Recommendation	Note
Environmental screening	Moderate	Conditional	Perform environmental sampling from surfaces (mattresses, beds, bedside tables, tables, chairs, armchairs, washbasins, window sills) that have been in contact with patients colonized or infected by *S. maltophilia*.
Antimicrobial stewardship (ABS)	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Healthcare-workers (HCWs) screening	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Chlorhexidine gluconate for patient bathing	NA		There is no evidence available to provide recommendations for, or against, the intervention.
Infection prevention and control (IPC) infrastructure	NA		There is no evidence available to provide recommendations for, or against, the intervention. However, the authors suggest provision of administrative support, including economic and human resources, to prevent and control *S. maltophilia* outbreak transmission.

HCW, healthcare worker; MDR, multidrug-resistant; NA: not available.

Approaches in Case of Transmission Control Failure

If control of transmission is not achieved by following the recommended measures, ward closure should be considered and additional epidemiological investigations should be performed, including searches for unusual environmental reservoirs which have epidemiological links to cases or may be using atypical transmission mechanisms.

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