REVIEW ARTICLE

Preventing the Spread of Multidrug-Resistant Gram-Negative Pathogens

Recommendations of an Expert Panel of the German Society for Hygiene and Microbiology

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SUMMARY

Background: Infections with multidrug-resistant gram-negative bacteria are hard to treat and cause high morbidity and mortality. The direct transmission of such pathogens is well documented, and measures to protect other patients would seem indicated. Nonetheless, evidence-based recommendations are not yet available because of insufficient data from clinical trials.

Methods: An expert panel was convened by two sections of the German Society for Hygiene and Microbiology (the permanent committee on general and hospital hygiene and the special committee on infection prevention and antibiotic resistance in hospitals) to review existing data on the epidemiology and diagnostic evaluation of multidrug-resistant gram-negative pathogens. The panel carried out a selective review of the relevant literature, with special attention to national guidelines.

Results and conclusion: In this paper, the expert panel presents a definition of multidrug-resistant gram-negative pathogens and recommends measures for preventing the spread of infection from colonized and infected patients in non-outbreak situations. These measures depend on the risk profile of the clinical setting. They are mostly to be considered “expert opinion,” rather than “evidence-based.”

► Cite this as:

Mattner F, Bange FC, Meyer E, Seifert H, Wichelhaus TA, Chaberny IF: Preventing the spread of multidrug-resistant gram-negative pathogens: recommendations of an expert panel of the German Society of Hygiene and Microbiology. *Dtsch Arztebl Int* 2012; 108(3): 39–45.
DOI: 10.3238/arztebl.2012.0039

The epidemiology of nosocomial infections has been documented in Germany for more than 10 years, as part of Germany’s Hospital Infection Surveillance System (German acronym KISS, Krankenhaus-Infektions-Surveillance-System) of the National Reference Centre (NRC) for the Surveillance of Nosocomial Infections. Other than *Staphylococcus aureus* (21.3% of infections), the most common pathogens causing nosocomial infections of the lower airways in intensive care units are gram-negative pathogens such as *Pseudomonas aeruginosa* (18.1%), *Klebsiella* spp. (12.6%), *Escherichia coli* (11.7%), and *Enterobacter* spp. (8.6%) (1).

Of particular significance is the increase in resistance to group 3 cephalosporins (G3C) among *Enterobacteriaceae*. The project Surveillance of Antibiotic Use and Bacterial Resistance in Intensive Care Units (German acronym SARI) shows that between 2001 and 2009 there was a steady increase in G3C-resistant *Escherichia coli* and *Klebsiella pneumoniae*, from 1.2% to 11.0% and from 3.8% to 12.5% respectively. The Figure shows the development of multidrug-resistant pathogens per 1000 patient days, split into methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), imipenem-resistant *Acinetobacter baumannii*, and G3C-resistant *Escherichia coli* and *Klebsiella pneumoniae* (2, 3).

Infections with multidrug-resistant gram-negative bacilli (MDR-GNB) are associated with mortality rates 21% higher than those of non-resistant GNB and result in longer inpatient stays and higher costs (e1–e5). The mortality rate of bacteremias in patients with *Klebsiella pneumoniae* caused by extended-spectrum beta-lactamase (ESBL)-producing pathogens is significantly higher than that of patients with non-ESBL-producing pathogens (64% versus 14%) (e6). It is particularly high during the first 25 days if the beginning of effective treatment is delayed (e7). The mortality rate of bacteremias caused by multidrug-resistant *Pseudomonas aeruginosa* is 30.7%, versus 17.8% for non-resistant *Pseudomonas aeruginosa* (e8). These infections are also associated with longer inpatient stays and higher costs (e9).

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FIGURE

Number of MDR pathogens per 1000 patient days

Incidence densities in 55 intensive care units involved in the SARI project.

Patients with multidrug-resistant (MDR) pathogens per 1000 patient days (2). SARI: surveillance of antibiotic use and bacterial resistance in intensive care units; MRSA: methicillin-resistant *Staphylococcus aureus*; VRE: vancomycin-resistant *Enterococcus faecium*; Imi R Aci: imipenem-resistant *Acinetobacter baumannii*; G3C R Kleb: Group 3 cephalosporin-resistant *Klebsiella pneumoniae*; G3C R Eco: Group 3 cephalosporin-resistant *Escherichia coli*

Transmission of MDR-GNB between patients is observed during outbreaks (e10–e12). There are few studies on transmission in endemic (i.e. non-outbreak) situations. In four studies, transmission of ESBL-producing pathogens was observed in 7 (5%) of 147 patients, 3 (13%) of 24 patients, 14 (52%) of 27 patients, and 5 (2.8%) of 177 patients (4, 5, e13, e14). The transmission density for ESBL-producing pathogens observed was 0.9 per 1000 exposure days (4.2 in hospitals, 0.4 in care homes) (4). The proportion of proven cases of multidrug-resistant gram-negative *Enterobacteriaceae* and non-fermenters in endemic situations that were caused by transmission was investigated in a further study, in 18 Dutch hospitals (6). This found MDR-GNB incidence densities of between 0.8 and 10.7 per 10 000 patient days, and transmission rates (the number of patients with suspected transmission of MDR-GNB as a proportion of the number of patients with non-nosocomially transmitted MDR-GNB) of between 0 and 15%.

Microbiological surveillance reveals an increase in carbapenem-resistant gram-negative pathogens in Europe as a whole. These “new” resistances, which have appeared only recently, pose a challenge for

microbiological diagnostics and infection control (7). Sampling of microbiological databases for carbapenem resistance in *E. coli* or *K. pneumoniae* seems to indicate, in our personal experience, that these remain very rare in Germany (8).

In addition to direct transmission, the spread of *Enterobacteriaceae* and non-fermenters is also partly determined by the pathogens’ environmental resistance. *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* can survive on surfaces for several days; *Acinetobacter baumannii* can do so for several weeks (9, 10, e15, e16).

Laboratory diagnostics of ESBL and other beta-lactamases

Enzyme inactivation by beta-lactamases is the most common cause of beta-lactam resistance in gram-negative pathogens. ESBL and species-specific AmpC beta-lactamases show a broader substrate spectrum that includes all cephalosporins as well as penicillins.

Resistance to carbapenems is caused by a loss of certain channel proteins of the outer membrane (porins), or by expression of carbapenem-hydrolyzing beta-lactamases (carbapenemases) (11).

Resistance in gram-negative pathogens is determined using standard tests. A distinction is drawn between phenotypic and genotypic methods (12, e17). A suspected diagnosis of ESBL is made when susceptibility to the indicator cephalosporins cefpodoxime, cefotaxime, ceftazidime, or ceftriaxone is limited. The diagnosis is confirmed via combined testing using the indicator cephalosporins and clavulanic acid. This partly restores the susceptibility that is limited in ESBL-producers (e18, e19).

Some automated systems provide a combination of screening and confirmation testing. In these cases no further testing is required (12, e20). There are several test systems available for phenotypic confirmation of AmpC beta-lactamases, metallo-beta-lactamases, and other carbapenemases. However, they do not always provide satisfactory specificity or sensitivity (7, 11, e21). PCR amplification and sequencing of beta-lactamase/carbapenemase genes (e.g. CTX-M, CMY, DHA, KPC, VIM, SHV, TEM, NDM-1) can now be used for precise genotypic identification of hydrolyzing enzymes. These tests are expensive and labor-intensive and are so far restricted to specialized laboratories.

The definition of multidrug-resistant gram-negative pathogens

The terms “multidrug-resistant” (MDR), “extensively drug-resistant” (XDR), and “pandrug-resistant” (PDR) are used frequently (13, 14). There are precise definitions of MDR and XDR for *Mycobacterium tuberculosis*, for example, and recently also for gram-negative pathogens (15, e22). The definition of multidrug resistance for gram-negative pathogens is a consensus definition provided by the ECDC (European Centre for Disease Prevention and Control) and CDC (Centers for Disease Control and Prevention) but is difficult for

physicians to apply in patient care, as it is highly complex.

A survey conducted in 2004 on the management of patients with MDR-GNB in German university hospitals showed that there were many different definitions of multidrug resistance in Germany, too (16).

One possible definition of multidrug resistance for *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* is based on evaluation of the four groups of antibiotics that have bactericidal effects: penicillins, cephalosporins, carbapenems, and fluoroquinolones. Aminoglycosides are not included, as they should only be used in combination therapy; nor are bacteriostatic antibiotics evaluated.

A pathogen is multidrug-resistant when only surrogate substances representing no more than one of these groups of antibiotics still yield a test result indicating susceptibility (17) (Table 1).

This definition also reflects the proposals included in a consensus recommendation for Baden-Württemberg (18) and those of a recently published definition of multidrug-resistant gram-negative pathogens by the German Commission for Hospital Hygiene and Infection Prevention (Kommission für Krankenhaushygiene und Infektionsprävention, KRINKO) (19). Testing and evaluation of antibiotic lead substances should identify epidemiologically frequent, clinically relevant resistance mechanisms in *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, as a basis for suggested hygiene measures in patient care.

For *Enterobacteriaceae* (e.g. *E. coli*, *Klebsiella spp.*), piperacillin/tazobactam or cefotaxime were selected as lead substances, because they are the most active antibiotics among the penicillins and cephalosporins, which have often been used in antibiotic treatment, and are used for resistance testing in most laboratories. Three lead substances are proposed for the carbapenems: imipenem and meropenem, because these are the most commonly used in therapy and are used for resistance testing in most laboratories; and ertapenem, because ertapenem testing is the most suitable method for detecting carbapenemase-producing pathogens. The carbapenem group is classified as resistant according to the result of intermediate testing of only one lead carbapenem, because in this event treatment may also fail when other carbapenems are administered, even though according to test results these others remained effective.

For *P. aeruginosa*, piperacillin or piperacillin/tazobactam were chosen as lead substances for the penicillins. Regardless of in vitro testing, in vivo the beta-lactamase inhibitor tazobactam does not usually improve the efficacy of piperacillin against *P. aeruginosa*. When these two antibiotics are tested, the results are the same as those of piperacillin alone. Ceftazidime and meropenem are the most effective cephalosporin and carbapenem respectively against *P. aeruginosa*. They were therefore selected as lead substances.

Within the *Acinetobacter* genus, *A. baumannii* is the most clinically and epidemiologically important

TABLE 1

Definition of multidrug resistance of gram-negative bacilli (MDR-GNB)

Penicillins	Cephalosporins	Carbapenems	Fluoroquinolones
Enterobacteriaceae (e.g. <i>E. coli</i> , <i>K. pneumoniae</i> , <i>E. cloacae</i>)			
Lead substance: piperacillin/ tazobactam* ¹	Lead substance: cefotaxime	Lead substance: imipenem, meropenem, or ertapenem* ¹	Lead substance: ciprofloxacin
R	R	S	R
R	R	R	S
R	S	R	R
R	R	R	R
Pseudomonas aeruginosa			
Lead substance: piperacillin or piperacillin/ tazobactam	Lead substance: ceftazidime	Lead substance: meropenem	Lead substance: ciprofloxacin
R	R	S	R
R	R	R	S
R	S	R	R
R	R	R	R
Acinetobacter baumannii * ²			
–	–	Lead substance: imipenem	Lead substance: ciprofloxacin
–	–	S	R
–	–	R	S
–	–	R	R

R: resistant; S: susceptible; –: insufficient efficacy

The table shows the possible patterns of distribution for multidrug-resistant pathogens with *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. Each line indicates a possible constellation. If only one or none of the four listed groups of antibiotics or their lead substances yields a test result indicating susceptibility, the pathogen is classified as multidrug-resistant.

The provided definition is valid for *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, but not for other gram-negative pathogens such as *Stenotrophomonas maltophilia*.

Intermediate test results are classified as resistant according to this definition.

When there is evidence of ESBL-producing enterobacteria, the penicillins and cephalosporins are classified as resistant according to the definition of MDR-GNB, even if efficacy can be demonstrated for individual members of these groups in vitro and possibly also in vivo.

ESBL-producing pathogens are only classified as multidrug-resistant if carbapenems and/or fluoroquinolones also yield a test result indicating resistance.

*¹If at least one of the lead substances yields an intermediate test result or a test result indicating resistance, the respective pathogen is classified as resistant to the whole group of antibiotics concerned. Imipenem resistance in *Proteus spp.*, *Providencia spp.*, and *Morganella spp.* should not be assessed.

*²For *Acinetobacter baumannii*: EUCAST establishes no limit values for evaluating susceptibility for either penicillins (with or without beta-lactamase inhibitors) or cephalosporins. The results of resistance testing for penicillins and cephalosporins are therefore not shown in this table.

TABLE 2

General hospital hygiene measures

Level	Measures
I	Standard hygiene
II	Level I plus barrier isolation; (disposable) gloves for all patient contact, patient-related gowns, patient-related care devices, separate bathroom facilities; patients may be accommodated in shared rooms
III	Level II plus transfer to single rooms or cohort isolation* ¹

*¹Cohort isolation should be based on cohorts of the same species if possible.

species. *A. baumannii* possesses inherent resistance to ampicillin and first- and second-generation cephalosporins. Beta-lactamase inhibitors, however, particularly sulbactam, are inherently active against *Acinetobacter baumannii*. Ampicillin/sulbactam may therefore be clinically effective in individual cases, as a result of sulbactam's intrinsic effect. However, according to the data of the European Committee on Antimicrobial Susceptibility Testing (EUCAST), the test results for penicillins are unreliable, and there are no clinical data available on beta-lactam/beta-lactamase combinations or on cephalosporins with which to assess efficacy. There are therefore no limit values established for assessing the susceptibility of penicillins, cephalosporins, or beta-lactam/beta-lactamase combinations. These groups of antibiotics are therefore not included in investigation of potential multidrug resistance of *A. baumannii*. Unlike *P. aeruginosa*, against *A. baumannii* imipenem is the most effective of all carbapenems and was therefore selected as the lead substance of the carbapenem group for *A. baumannii*.

Ciprofloxacin is the most effective fluoroquinolone against *Enterobacteriaceae*, *P. aeruginosa*, and *A. baumannii* and was therefore chosen as the lead substance for all groups of pathogens.

Preventing and controlling the spread of multidrug-resistant gram-negative pathogens

There are currently no comprehensive controlled studies available that can be used to assess additional hygiene measures according to evidence-based criteria (e23). What follows is based on individual studies and expert opinions.

Active screening

Examples of active screening are examination of particular groups of patients on admission or examination of contact patients. In a Swiss study, active screening revealed a prevalence of ESBL-producing pathogens of 18% in high-risk patients (previous inpatient stay abroad, country of origin with high ESBL prevalence rates) (4). Research from Israel and Saudi Arabia shows colonization rates ranging from 10% to 26% (e24, e25).

ESBL-producing pathogen prevalence rates of 51% have been found among the residents of several care homes in Ireland (e26). Screening on admission to intensive care units (ICUs) in a university hospital in southern Germany showed colonization rates of 3% to 9% (20). However, some studies in endemic situations showed no decrease in the spread of MDR-GNB as a result of active screening (6, e27–e29).

The guideline of the US Healthcare Infection Control Practices Advisory Committee (HICPAC) on handling multidrug-resistant microorganisms in medical care does not provide a definite recommendation on active screening (21), while the Dutch guideline on highly-resistant pathogens recommends active screening in selected patients (14). The CDC's recommendations on active screening, meanwhile, so far address only carbapenem-resistant *Enterobacteriaceae* (22). As an estimate of whether a particular hospital poses a risk to patients of infection with carbapenem-resistant *Enterobacteriaceae*, examination of microbiological results from the past 6 to 12 months for evidence of carbapenem-resistant *Enterobacteriaceae* is recommended. The CDC also recommends active screening following contact with patients with these multidrug-resistant pathogens (22). Active screening, in addition to other multimodal infection control measures, has made it possible to control several outbreaks of carbapenem-resistant *Enterobacteriaceae* (e24, e28, e29).

Active screening is accepted for contacts of patients with carbapenem-resistant gram-negative pathogens (*Enterobacteriaceae* and *Acinetobacter baumannii*) and should also be considered on admission for patients from high-risk countries (4, 5). It remains unclear whether it should also be performed routinely in cases of MDR-GNB. This should be determined on the basis of prevalence in individual regions (e30).

Future studies should investigate which patient materials and which methods of microbiological testing are most appropriate for screening. In very general terms, swabs should be taken from open wounds and tracheal secretions of patients receiving ventilation should be tested. In addition, perianal/rectal swabs for evidence of intestinal colonization by *Enterobacteriaceae*, *Acinetobacter baumannii*, or *Pseudomonas aeruginosa* can also be recommended.

Isolation measures

The HICPAC's guideline recommends isolation in individual rooms or cohorts for cases of MDR-GNB (21). In addition to hand hygiene with alcohol hand rub, gowns and gloves should be worn during contact with patients. Mouth and nose protection is required in situations in which droplets are formed (e.g. bronchoscopies). In outpatient care, standard hygiene measures are considered sufficient. These recommendations are adopted in the document *Guidance for Control of Infections with Carbapenem-Resistant or Carbapenemase-Producing Enterobacteriaceae in Acute Care Facilities*, recently published by the CDC and HICPAC (22).

TABLE 3

Hygiene measures for multidrug-resistant gram-negative bacilli (MDR-GNB) and ESBL-producing pathogens in hospitals

Pathogens	Hygiene measures (Table 2)			Comments
	Level I	Level II	Level III	
ESBL-producing <i>E. coli</i> and <i>Klebsiellae</i> that remain susceptible to fluoroquinolones and carbapenems	Standard wards and at-risk areas ^{*1}	Not necessary	Not necessary	This is a minimum recommendation; stricter procedures may be advisable, e.g. for non-multidrug-resistant ESBL-producing <i>Klebsiella pneumoniae</i> , according to information on outbreaks described several times involving non-multidrug-resistant MDR pathogens (e11, e35–e48) and varying levels of transmissibility.
MDR-GNB	Insufficient	Standard wards if single rooms unavailable	Always in at-risk areas ^{*1}	
Carbapenem-resistant MDR-GNB: <i>Enterobacteriaceae</i> and <i>Acinetobacter baumannii</i>	Insufficient	Insufficient	Always	May lead to hard-to-control outbreaks; isolation measures are also effective in reducing prevalence (25, e49–e51).
MDR-GNB with resistance to all four groups of antibiotics	Insufficient	Insufficient	Always	

^{*1} e.g. intensive care units, intermediate care wards, areas with severely immunosuppressed patients such as hematology/oncology and neonatology. Level III hygiene measures must always be implemented in the event of an outbreak, regardless of resistance profile.

The Dutch guideline recommends isolation measures for all patients with MDR-GNB (14) and distinguishes between type of pathogen, degree of resistance, and area of hospital care: For MDR-GNB in not-at-risk areas, barrier isolation is accepted even without patients being transferred to single rooms. For ESBL-producing pathogens or resistance to carbapenem, single rooms are always recommended. If single rooms are unavailable, barrier isolation may be used; care devices (e.g. dressings) is to be used for one patient only and must never be used between patients, and gloves should be worn for all patient contact. If the pathogen is present in oropharyngeal materials, mouth and nose protection is also recommended. If there is evidence of multidrug-resistant *Acinetobacter baumannii*, all the above-mentioned measures are always required. A seven-year observational study showed that *Acinetobacter baumannii* was detected more frequently when individual or cohort isolation and the use of gowns and gloves during care were not adopted. After these measures were reintroduced the detection rate fell to its original level (e31).

No controlled studies have demonstrated the efficacy of the measures recommended by the HICPAC. However, because of the increasing prevalence rates of MDR-GNB in Germany recommendations on effective hygiene measures are urgently needed. A first step in this direction has been taken by a group of hygiene specialists for Baden-Württemberg (18).

In the suggestions made here, we are attempting to develop hygiene standards in line with the degree of resistance and type of inpatient care. A distinction is drawn between standard hygiene measures; further measures involving gowns, gloves, patient-related care

devices, and individual bathroom facilities (barrier isolation); and isolation in single rooms or cohort isolation (Tables 2 and 3). A high level of compliance with hand hygiene is just as essential as responsible use of antibiotics (23).

It is unlikely that a patient will be cured of a MDR-GNB during his/her inpatient stay, which would allow isolation measures to be discontinued. Long-term colonization was observed in 33 residents of a care home, with an average of 144 days (41 to 349 days). Two thirds of colonized residents had been colonized by more than two different multidrug-resistant species. Spontaneous cure was observed in only three residents (9%) (e32). *Acinetobacter baumannii* and *Pseudomonas aeruginosa* colonization times are also long (e33). As it remains unclear whether and how patients can be decolonized, no recommendations can currently be made on discontinuing specific hygiene measures. Some of the above-mentioned guidelines recommend discontinuing isolation measures after repeat negative swab results (14, 18). This can be accepted pragmatically. We also believe it advisable to label patients' medical records (e.g. as part of an alert system similar to that for MRSA patients) (e34), so that if patients are readmitted screening cultures can be done and patients can be isolated, if necessary.

Laboratory surveillance and surveillance of affected patients

Because MDR-GNB are a major problem, both sporadic and epidemic cases must be identified promptly (1, 24). The first resource for this is the list of pathogens with particular resistance and multidrug resistance according to section 23 of the German Law on Protection Against Infection, which is available

from laboratories. It is advisable to use the definitions proposed here (*Table 1*) to detect MDR-GNB, to record them separately in the statistics, and to report cases to hygiene staff. MDR-GNB can be recorded for individual departments in order to determine frequencies. Ideally, even a single case should be reported directly to hygiene staff, so that hygiene measures can be promptly recommended.

On this basis, active surveillance must be performed by hygiene staff, according to standard definitions. This makes it possible to distinguish between nosocomial infections/colonizations and those acquired outside the hospital. These can be related to denominator data (patient days or number of patient admissions) to provide standardization, and therefore reliable evaluation of epidemiological trends (5).

To provide information on transmission, molecular genetic typing of pathogens and perhaps identification of resistance mechanisms may be required to clarify epidemiological correlations and possible sources of infection.

Acknowledgements

We would like to express our sincere gratitude to Prof. Dr. rer. nat. Dr. med. Wilfried Bautsch, PD Dr. med. Axel Kola, and Dr. rer. nat. Yvonne Pfeifer for their active collaboration and constructive discussions.

All the authors are members of the German Society for Hygiene and Microbiology (Deutsche Gesellschaft für Hygiene und Mikrobiologie, DGHM).

We would like to thank all the other members of the German Society for Hygiene and Microbiology (Deutsche Gesellschaft für Hygiene und Mikrobiologie, DGHM) for their support.

Conflict of interest statement

Prof. Chaberny has received reimbursement of expenses from Mönlycke Healthcare, and lecture fees from Roche Diagnostik, DADE Behring, and Siemens.

Prof. Wichelhaus has received consultancy fees from Almirall and Novartis, and lecture fees from Pfizer and Novartis.

Prof. Seifert acts as a consultant to Astellas, Astra Zeneca, and Novartis. He receives consultancy fees from Pfizer, Basilea, Novartis, Bayer, Janssen-Cilag, and Astellas. He has received reimbursement of expenses for conference participation and travel expenses from Pfizer, Novartis, and Astellas and lecture fees from Bayer, Gilead, Janssen-Cilag, Infectopharm, MSD, Novartis, Pfizer, and Astellas. He has accepted monies paid into a third-party account from Astellas, Basilea, Bayer, Novartis, and Pfizer.

All other authors declare that no conflict of interest exists.

Manuscript received on 1 May 2011, revised version accepted on 24 October 2011.

Translated from the original German by Caroline Devitt, MA.

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KEY MESSAGES

- Only the four groups of bactericidal antibiotics (penicillins, cephalosporins, carbapenems, and fluoroquinolones) are used to determine multidrug resistance of gram-negative bacteria. A bacterium is multidrug-resistant when only lead substances representing no more than one of these groups of antibiotics still yield a test result indicating susceptibility.
- It remains unclear whether active screening of contacts of MDR-GNB patients should be recommended. This should be decided on the background of prevalence in individual regions.
- Routine isolation measures for patients with MDR-GNB are advisable. Barrier isolation and isolation in single rooms or cohort isolation are implemented on the basis of inpatient risk areas.
- Laboratory surveillance according to section 23 of the German Law on Protection Against Infection must be performed on the basis of the proposed definition of multidrug resistance.
- According to section 23 of the revised German Law on Protection Against Infection, active surveillance should be performed by hygiene staff according to standard definitions.

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REVIEW ARTICLE

Preventing the Spread of Multidrug-Resistant Gram-Negative Pathogens

Recommendations of an Expert Panel of the German Society for Hygiene and Microbiology

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