Laboratory diagnosis, clinical management and infection control of the infections caused by extensively drug-resistant Gram-negative bacilli: a Chinese consensus statement


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Abstract

Extensively drug-resistant (XDR) Gram-negative bacilli (GNB) are defined as bacterial isolates susceptible to two or fewer antimicrobial categories. XDR-GNB mainly occur in Enterobacteriaceae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Stenotrophomonas maltophilia. The prevalence of XDR-GNB is on the rise in China and in other countries, and it poses a major public health threat as a result of the lack of adequate therapeutic options. A group of Chinese clinical experts, microbiologists and pharmacologists came together to discuss and draft a consensus on the laboratory diagnosis, clinical management and infection control of XDR-GNB infections. Lists of antimicrobial categories proposed for antimicrobial susceptibility testing were created according to documents from the Clinical Laboratory Standards Institute (CLSI), the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the United States Food and Drug Administration (FDA). Multiple risk factors of XDR-GNB infections are analyzed, with long-term exposure to extended-spectrum antimicrobials being the most important one. Combination therapeutic regimens are summarized for treatment of XDR-GNB infections caused by different bacteria based on limited clinical studies and/or laboratory data. Most frequently used antimicrobials used for the combination therapies include aminoglycosides, carbapenems, colistin, fosfomycin and tigecycline. Strict infection control measures including hand hygiene, contact isolation, active screening, environmental surface disinfections, decolonization and restrictive antibiotic stewardship are recommended to curb the XDR-GNB spread.

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Keywords: Enterobacteriaceae infection, multidrug resistant (MDR), pandrug resistant (PDR), XDR, XDR Acinetobacter infection, XDR Pseudomonas aeruginosa infection

Original Submission: 1 June 2015; Revised Submission: 6 November 2015; Accepted: 6 November 2015

Editor: M. Paul

Article published online: 25 November 2015

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http://dx.doi.org/10.1016/j.cmi.2015.11.004
Introduction

Bacterial resistance to antibiotics has become one of the major threats of human health (http://www.cdc.gov/drugresistance/threat-report-2013/index/html). Extensive drug resistance (XDR) refers to the phenomenon in some bacteria that shows resistance to nearly all antimicrobial agents available except one or two. XDR emerges primarily in Gram-negative bacilli (GNB), especially Enterobacteriaceae, Acinetobacter baumannii, Pseudomonas aeruginosa and Stenotrophomonas maltophilia. For the infections caused by XDR bacteria, efficacious treatment is limited, and no data are available from large series of randomized clinical studies at the present time. Antimicrobial monotherapy, including the old drug polymyxin and the newer antibiotic tigecycline, usually cannot provide satisfactory efficacy. Combination antimicrobial therapy is used in most cases. XDR infection mostly develops in patients with severe underlying disease, immunodeficiency and/or repeated long-term use of broad-spectrum antimicrobial agents and is associated with poor clinical outcome. As a consequence, XDR has become one of the most troublesome issues in current management of bacterial infections. This consensus statement was formulated after back-and-forth discussion and consultation with relevant clinical experts, microbiologists and pharmacologists who are working in the field of infectious diseases in China to help improve the clinical management of XDR bacterial infections.

Definitions

An expert consensus on MDR, XDR and pandrug-resistant (PDR) bacteria was proposed in 2012 via a joint initiative of the European Centre for Disease Prevention and Control (ECDC) and the US Centers for Disease Control and Prevention (CDC), involving the relevant experts from the United States and many European countries [1]. This expert consensus is now widely referenced in China and other countries to define bacterial resistance.

Multidrug resistant (MDR)
The isolate is nonsusceptible to at least three antimicrobial categories within its susceptibility spectrum (including resistant and intermediate). Resistance to one antimicrobial category is defined when the isolate is nonsusceptible to at least one agent in the recommended list for susceptibility testing of the corresponding category.

Extensively drug resistant (XDR)
The isolate is nonsusceptible to all but two or fewer antimicrobial categories (mainly polymyxin and tigecycline). The determination of resistance to one antimicrobial category is the same as for MDR.

Pandrug resistant (PDR)
The isolate is nonsusceptible to all agents in all the antimicrobial categories in current clinical use.

The concepts of PDR and XDR are dynamic and changing as a result of the available antimicrobial categories, which vary with time and country. For example, after tigecycline was launched for clinical use, the previous PDR strains of A. baumannii could become XDR if susceptible to tigecycline.

Determination of antimicrobial-resistant phenotypes

Disk diffusion, agar dilution and broth microdilution susceptibility testing methods as well as other commercial testing systems are used in clinical microbiology laboratories to determine the antimicrobial-resistant phenotypes of clinical isolates so as to identify it as a MDR, XDR or PDR strain. The minimum inhibitory concentration (MIC) values of antimicrobial agents or the diameter of inhibition zone in disk diffusion testing should be determined for XDR strains if possible to provide the basis for selection of antimicrobial agents and the dosage in combination antimicrobial therapy.

Lists of antimicrobial categories proposed for antimicrobial susceptibility testing of various bacterial types and the corresponding breakpoints for interpretation of susceptibility testing results usually follow the guidelines of the Clinical Laboratory Standards Institute (CLSI) [2], the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (http://www.eucast.org/clinical_breakpoints/) and the United States Food and Drug Administration (FDA). Cefoperazone–sulbactam is one of the most commonly used antimicrobials for the treatment of Acinetobacter spp. infections and routinely tested in China. The breakpoints of cefoperazone–sulbactam usually follow the recommendation of Jones et al. [3]: susceptible (S), ≤16/8 mg/L; intermediate (I), 32/16 mg/L; and resistant (R), ≥64/32 mg/L.

The recommended antimicrobial categories and agents for testing various common XDR-GNB are presented in Table 1 (http://www.eucast.org/clinical_breakpoints/) [2].

Some of the special mechanisms underlying bacterial resistance are predictive of the possibility of XDR. For example, production of carbapenemase is the main mechanism of carbapenem resistance in Enterobacteriaceae. At present, carbapenemase production is primarily detected by phenotype testing and molecular biologic methods. Phenotype testing methods include modified Hodge test, inhibitor-based method and double-disk synergy test. Phenotype testing methods are simple to operate, practical, cost-effective and convenient for routine testing, but the results cannot be available quickly
because of the longer time required for bacterial growth. Additionally, such methods cannot provide the specific type of carbapenemase and related information. PCR-based sequence analysis of the carbapenemase gene is now the recognized reference standard test of carbapenemase. In addition, the commercial microarray chips or matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry (MALDI-TOF) can also be used to detect carbapenemases.

**Mechanisms of antibiotic resistance in XDR-GNB**

The XDR phenotype of *Enterobacteriaceae* is primarily due to production of carbapenemase [4–6]. Such XDR strains may have other mechanisms of resistance to antibiotics such as production of extended spectrum β-lactamases [5], AmpC β-lactamase, expressing efflux pump [6] or porin mutation [7]. In China, the commonest type of carbapenemase produced by *Enterobacteriaceae* strains is class A carbapenemase KPC (KPC-2), and metalloenzyme IMP, VIM and NDM-1 enzymes are reported sporadically.

The mechanisms of the antibiotic resistance in *A. baumannii* are also very complex, usually involving multiple mechanisms simultaneously, including production of multiple β-lactamases, reduced membrane permeability and increased expression of efflux pump [8]. Its XDR phenotype is primarily attributed to expressing various carbapenemases. Studies on the clinical strains isolated in our country have found that the carbapenemases produced by *A. baumannii* mainly include OXA-type enzymes (predominately OXA-23-like), metalloenzymes (IMP, VIM and NDM) and Ambler class A β-lactamases (KPC and GES) [9], as well as increased expression of efflux pump (AdeABC).

The XDR of *P. aeruginosa* usually results from the joint effects of multiple mechanisms of resistance [10,11], including production of multiple β-lactamases (especially carbapenemases), high-level expression of efflux pumps, target modification and alteration of outer membrane proteins. The formation of biofilm also has an important effect on the in vivo susceptibility to antimicrobial agents. In China, resistance of *P. aeruginosa* strains to carbapenems is primarily due to the loss of porin (OprD2) and high expression of efflux pump (Mex-Opr), as well as production of metalloenzymes (e.g. IMP, VIM and NDM).

*S. maltophilia* strains show intrinsic resistance to multiple antimicrobial categories including carbapenems. These strains also have multiple other mechanisms of acquired resistance mediated by chromosomes, plasmids, transposons or integrons, including production of multiple β-lactamases, multidrug efflux pumps, class I integron and Insertion sequence common region (ISCR) elements associated with resistance to trimethoprim–sulfamethoxazole (TMP-SMX), phosphoglucomutase (SpgM) associated with resistance to multiple antimicrobial agents, reduction in outer membrane permeability, SmQnr determinants associated with resistance to quinolones and mutations of bacterial gyrase genes [12,13].

**Epidemiology of XDR-GNB**

The data of CHINET, a bacterial resistance surveillance network in China, showed that XDR-GNB strains in China are mainly found in *A. baumannii*, *Klebsiella pneumoniae* and *P. aeruginosa*. During 2008 to 2014, the prevalence of XDR strains in *A. baumannii* and *K. pneumoniae* increased from 10.9% to 19.7% and from 0.3% to 3.2%, respectively, whereas XDR *P. aeruginosa* decreased slightly from 2.1% to 1.6% [14]. During 2005–2014, the imipenem resistance rates in *K. pneumoniae* increased from 2.4% to 10.5%, while in *Escherichia coli*, the resistance rates were stable (approximately 1%). The imipenem resistance rates in *A. baumannii* increased from 31% to 62.4%, whereas the imipenem resistance rate in *P. aeruginosa* decreased from 31% to 26.6% during this time [15]. The prevalence and phenotypic characteristics of carbapenem-resistant *E. coli* and *K. pneumoniae* and of XDR *P. aeruginosa* and *A. baumannii* isolated from blood cultures in China are addressed elsewhere in this issue [16].

**Risk factors and clinical characteristics of XDR-GNB infections**

The single most important risk factor for extensive resistance in GNB is long-term exposure to antimicrobial agents, especially extended-spectrum antimicrobial agents [17]. Cephalosporins and other antimicrobial agents are used to supplement animal feed stuff in some regions, which increases the resistance of the colonizing bacteria in animals, especially *Enterobacteriaceae*, which may facilitate the spread of resistant bacteria [18]. The other risk factors leading to emergence of resistance are explained below, with specific microorganisms.

**XDR *Enterobacteriaceae* infection**

The most common species of XDR *Enterobacteriaceae* is *K. pneumoniae*, followed by *E. coli*. These strains usually cause infections of lungs, urinary tract and bloodstream, as well as skin and soft tissue. The risk factors for XDR *Enterobacteriaceae* infections include critical underlying diseases, previous use of
antimicrobial agents, stay in the intensive care unit (ICU), solid organ or blood transplantation, surgical operation and catheterization, and indwelling drainage tube. XDR Enterobacteriaceae strains may colonize the intestinal tract for a long time (up to several months) and result in spread of the resistant strain in the hospital. Some of the colonizing bacteria may finally evolve to clinical infection [19,20].

XDR Acinetobacter infection

XDR Acinetobacter strains are mostly found in hospital-acquired pneumonia (HAP), mainly in ICU patients under mechanical ventilation. Recently, an epidemiologic survey on HAP conducted in China showed that Acinetobacter spp. was the most common pathogen of HAP and that 76.8% of the Acinetobacter strains causing HAP were resistant to carbapenems [21]. Acinetobacter strains isolated from sputum should be differentiated to infection or colonization. A. baumannii-related bloodstream infection is usually the result of pulmonary or abdominal infection, or device-related infections. Efforts should be made to identify the primary source of infection and possible secondary sites of infection. Skin and soft tissue infections caused by A. baumannii mainly occur in patients with diabetes mellitus or other underlying diseases, or a history of surgery or trauma, especially those with a history of trauma and water contact. A study suggested that XDR A. baumannii-related infection of central nervous system may be acquired via the respiratory tract, especially with ventilators, in addition to invasive procedures such as surgery [22]. Risk factors for XDR A. baumannii infection include general anesthesia, stay in ICU, prior hospitalization, and prior use of multiple classes of antimicrobial agents [22].

XDR P. aeruginosa infection

Infections caused by P. aeruginosa are mostly pulmonary, bloodstream, skin and soft tissue, abdominal and urinary tract infections. The predisposing factors for XDR P. aeruginosa infections include chronic obstructive pulmonary disease, long hospital stay before infection, mechanical ventilation, critical disease (Acute Physiology and Chronic Health Evaluation (APACHE) II score >16) and inappropriate antimicrobial monotherapy [23,24]. A study indicated that prior use of fluoroquinolones was one of the independent risk factors for emergence of XDR P. aeruginosa infection [24].

XDR S. maltophilia infection

In 2004, 17 PDR strains of S. maltophilia were isolated from a hospital in Taiwan. The MIC ranges of tigecycline, TMP-SMX and levofloxacin against these strains were 4–32, 8–32 and 16–64 mg/L, respectively. Seven strains were isolated from patients with infections (six from pneumonia and one from bile tract infection), and the remaining ten strains were from colonized patients. For 12 of the 17 PDR S. maltophilia strains, non-PDR S. maltophilia strains had been isolated before the emergence of pandrug resistance, which suggests that the antimicrobial resistance was selected by antimicrobial therapy. Mortality of the patients with PDR-strain infection was higher
Antimicrobial therapy for XDR-GNB infection

Principles of antimicrobial therapy of XDR-GNB infection
1. When a strain of XDR-GNB is isolated from clinical specimens, especially XDR A. baumannii or S. maltophilia, a distinction should be made between infection and colonization.
2. Appropriate effective antimicrobial agents should be selected according to the results of susceptibility testing. When the strain is nonsusceptible to all the antimicrobial agents tested, the agents showing intermediate or inhibition zone or MIC value closer to the breakpoints of susceptibility (or intermediate) for that strain may be selected for combination therapy at a higher dosage.
3. Combination therapy is usually used to manage XDR-GNB infections.
4. The dosing regimen should be designed according to pharmacokinetic and pharmacodynamic profiles, e.g. higher dose and/or longer duration of intravenous infusion for β-lactams such as carbapenems, high maximum concentration (C\text{max}) and/or area under the curve/MIC or C\text{max}/MIC values for quinolones and aminoglycosides.
5. The dose of antimicrobial therapy should be adjusted appropriately in patients with hepatic or renal impairment and elderly patients.
6. Every effort should be made to eliminate the risk factors of infection and control of infection source, and to actively address the primary disease.

Selection of antimicrobial agents for XDR-GNB infections
A limited number of antimicrobial agents are now available for XDR-GNB infections. Considering the in vitro susceptibility, tigecycline and polymyxins are the most active for XDR-GNB; however, limited clinical studies indicate that high rate of clinical failure is observed with tigecycline or polymyxin monotherapy. Combined antimicrobial therapy (two- or three-drug combinations) is usually used to manage XDR-GNB infections, largely on the basis of case reports, case series or small cohort studies; solid evidence is needed to justify the advantage of combination therapy [28] (Table 2).

Common antimicrobial agents for treatment of XDR-GNB infections

Aminoglycosides. Studies indicate that aminoglycosides alone have achieved favourable efficacy in treating carbapenem-resistant K. pneumoniae infections, 80% of which are bloodstream infections [19]. The antibiotics of this category are usually combined with other antimicrobial agents to treat infections caused by XDR Enterobacteriaceae, P. aeruginosa or A. baumannii [29–31]. A dose of 15 mg/kg per day is recommended for amikacin or isepamicin in many countries, but in China the dose is lower because therapeutic drug monitoring for aminoglycosides has not yet been implemented. For patients with severe infection and normal renal function, 0.8 g/day once daily is recommended. Considering the increasing use of aminoglycosides in the treatment of MDR and XDR bacterial infections, a relatively high dose is recommended; the establishment of aminoglycoside therapeutic drug monitoring methods and implementation in clinical use are needed in countries where aminoglycoside therapeutic drug monitoring has not yet been used.

Carbapenems. Time-kill assays revealed antimicrobial synergism for imipenem in combination with colistin (75%), tigecycline (50%), ampicillin/sulbactam (42%) and amikacin (42%) for carbapenem-resistant A. baumannii [32]. Several clinical studies have suggested that carbapenems in combination with other antimicrobial agents such as polymyxins are associated with better efficacy for carbapenem-resistant Enterobacteriaceae (CRE) infections than carbapenem monotherapy or other antimicrobial combinations [19,33–35]. Studies indicate that carbapenems can be used in a high-dose (e.g. meropenem 2 g every 8 hours), prolonged-infusion (2–3 hours) regimen to treat infections caused by carbapenem-resistant K. pneumoniae strains with MICs of ≤8 mg/L [19,34,36]. If possible, exact carbapenem MIC value or inhibition zone are welcome to be reported for XDR- or PDR-GNB for determining whether carbapenems can be used in combination therapy. Meropenem and imipenem are the commonly used carbapenems, but ertapenem because it is not active against A. baumannii and P. aeruginosa, with a low recommended dose of 1 g once a day. They are usually used in combination with polymyxins, tigecycline, fosfomycin or rifampicin [32,37].
**TABLE 2. Combination antimicrobial therapies described for extensively drug-resistant (XDR) Gram-negative bacilli infections**

<table>
<thead>
<tr>
<th>Infection</th>
<th>Two-drug combination</th>
<th>Three-drug combination</th>
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<tr>
<td><strong>XDR Enterobacteriaceae</strong></td>
<td>Tigecycline-based combinations:</td>
<td>Tigecycline + polymyxin + carbapenems&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>[19,31,40,59,60]</td>
<td>- Tigecycline + aminoglycosides&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td>- Tigecycline + carbapenems&lt;sup&gt;c&lt;/sup&gt;</td>
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<td></td>
<td>- Tigecycline + fosfomycin</td>
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<td></td>
<td>- Tigecycline + polymyxin</td>
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<td></td>
<td>Polymyxin-based combinations:</td>
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<tr>
<td></td>
<td>- Polymyxin + carbapenems</td>
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<td></td>
<td>- Polymyxin + tigecycline</td>
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<td></td>
<td>- Polymyxin + fosfomycin</td>
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<td></td>
<td>Other combinations:</td>
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<td></td>
<td>- Fosfomycin + aminoglycosides&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td>- (ceftazidime or cefepime) + amoxicillin–clavulanic acid</td>
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<td></td>
<td>- Aztreonam + aminoglycosides&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td><strong>XDR Acinetobacter baumannii</strong></td>
<td>Combinations based on sulbactam or its fixed-dose combination:</td>
<td>Cefoperazone–sulbactam + tigecycline + carbapenems&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>[42,49,54,55,64]</td>
<td>- (cefoperazone–sulbactam or ampicillin–sulbactam) + tigecycline</td>
<td>- Cefoperazone–sulbactam + doxycline + carbapenems&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>- Sulbactam + carbapenems&lt;sup&gt;e&lt;/sup&gt;</td>
<td>- Imipenem + rifampicin (polymyxin or tobramycin)</td>
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<td></td>
<td>- Tigecycline-based combinations:</td>
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<td></td>
<td>- Tigecycline + (cefoperazone–sulbactam or ampicillin–sulbactam)</td>
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<td></td>
<td>- Tigecycline + carbapenems&lt;sup&gt;e&lt;/sup&gt;</td>
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<td></td>
<td>- Tigecycline + polymyxin</td>
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<td>Polymyxin-based combinations:</td>
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<td></td>
<td>- Polymyxin + carbapenems&lt;sup&gt;e&lt;/sup&gt;</td>
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<td></td>
<td>- Polymyxin + tigecycline</td>
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<td><strong>XDR Pseudomonas aeruginosa</strong></td>
<td>Polymyxin-based combinations:</td>
<td>Polymyxin + antipseudomonal β-lactams&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
<td>[29,30,40,43]</td>
<td>- Polymyxin + antipseudomonal β-lactams&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>- Polymyxin + ciprofloxacin</td>
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<td></td>
<td>- Polymyxin + fosfomycin</td>
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<td>- Polymyxin + rifampicin</td>
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<td></td>
<td>Antipseudomonal β-lactams-based combinations:</td>
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<td></td>
<td>- Antipseudomonal β-lactams&lt;sup&gt;d&lt;/sup&gt; + aminoglycosides&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td>- Antipseudomonal β-lactams&lt;sup&gt;d&lt;/sup&gt; + ciprofloxacin</td>
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<td></td>
<td>- Antipseudomonal β-lactams&lt;sup&gt;d&lt;/sup&gt; + fosfomycin</td>
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<td>Ciprofloxacin-based combinations:</td>
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<td></td>
<td>- Ciprofloxacin + antipseudomonal β-lactams&lt;sup&gt;d&lt;/sup&gt;</td>
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<td></td>
<td>- Ciprofloxacin + aminoglycosides&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Combination of two β-lactams:</td>
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<tr>
<td></td>
<td>- (ceftazidime or aztreonam) + piperacillin–tazobactam</td>
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<td></td>
<td>- Ceftazidime + cefoperazone–sulbactam</td>
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<td></td>
<td>- Aztreonam + ceftazidime</td>
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<td><strong>XDR Stenotrophomonas maltophilia</strong></td>
<td>Trimethoprim–sulphamethoxazole-based combinations:</td>
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<tr>
<td>[45,46,51]</td>
<td>- Trimethoprim–sulphamethoxazole + (ceftazidim–clavulanic acid or cefoperazone–sulbactam)</td>
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<td></td>
<td>- Trimethoprim–sulphamethoxazole + fluoroquinolones&lt;sup&gt;i&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>- Trimethoprim–sulphamethoxazole + minocycline</td>
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<td>- Trimethoprim–sulphamethoxazole + ceftazidime</td>
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<td></td>
<td>- Trimethoprim–sulphamethoxazole + polymyxin</td>
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<td>Quinolones-based combinations:</td>
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<td></td>
<td>- Fluoroquinolones + trimethoprim–sulphamethoxazole</td>
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<td></td>
<td>- Fluoroquinolones + (ceftazidim–clavulanic acid or cefoperazone–sulbactam)</td>
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<td>- Fluoroquinolones + ceftazidime</td>
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<td>Polymyxin-based combinations:</td>
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<td></td>
<td>- Polymyxin + (ticarcillin–clavulanic acid or cefoperazone–sulbactam)</td>
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<td></td>
<td>- Polymyxin + trimethoprim–sulphamethoxazole</td>
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<sup>a</sup>Aminoglycosides include amikacin, isepamicin, etc.

<sup>b</sup>Carbapenems include meropenem, imipenem, etc. (not ertapenem).

<sup>c</sup>Most data are from in vitro studies or case reports of multidrug resistant or XDR P. aeruginosa. Data from clinical studies are limited for combination therapies.

<sup>d</sup>Antipseudomonal β-lactams refer to the β-lactams active against P. aeruginosa, such as carbapenems (meropenem, imipenem), ceftazidime, aztreonam, piperacillin–tazobactam and cefoperazone–sulbactam.

<sup>e</sup>Most data are from in vitro studies or case reports of multidrug-resistant S. maltophilia. The data from clinical studies are limited for combination therapies.

<sup>f</sup>Fluoroquinolones include ciprofloxacin, levofloxacin and moxifloxacin.

Fosfomycin. The majority (95%) of the carbapenemase-producing Enterobacteriaceae strains are susceptible to fosfomycin. Most (83%) of the metalloenzyme-producing strains are also susceptible to fosfomycin [38]. In China, approximately 40% of the CRE isolates were sensitive to fosfomycin [39]. Intravenous fosfomycin can be used in combination with polymyxin, tigecycline, carbapenems and aminoglycosides to treat carbapenemase-producing XDR or PDR K. pneumoniae and P. aeruginosa infections, with a clinical success rate of 54.2% and bacterial eradication rate of 56.3% in 48 ICU patients. The main adverse event was reversible hypokalaemia [40]. Fosfomycin resistance can develop during therapy, supporting the idea of using this agent in combination [40,41]. The dosing regimen of fosfomycin is 8 g every 8 hours or 6 g every 6 hours by intravenous infusion. Clinical studies are currently limited in this respect. Both oral and intravenous fosfomycin are available...
in China, and intravenous preparation is commonly used for the treatment of methicillin-resistant *Staphylococcus aureus* and *Enterococcus* infections in combination with vancomycin. Use of fosfomycin is increasing in XDR-GNB infections.

**Polymyxins.** This category of antibiotic includes polymyxin B and polymyxin E (colistin). Polymyxins have good in vitro activity against various highly resistant Gram-negative clinical isolates. Synergistic antimicrobial effect is observed when it is combined with carbapenems, quinolones, piperacillin–tazobactam, tigecycline or doxycycline [29,30,42–44]. Approximately 68% to 79% of *S. maltophilia* isolates are susceptible to polymyxins [44,45]. However, only 37.5% of MDR strains are susceptible [46]. Polymyxin is mainly used to treat various XDR-GNB infections. There is apparent heterogeneous resistance to polymyxins in these Gram-negative strains [47]. The mutation prevention concentration of polymyxins is high for *A. baumannii* [48]. Polymyxins are usually used in combination with carbapenems, tigecycline or fosfomycin [47]. For the elderly and the patients with reduced renal function, special attention should be taken to monitor renal function.

The recommended dosages of polymyxin E (colistimethate sodium, CMS) are 2.5–5.0 mg/kg per day of colistin-base activity (CBA) provided by intravenous infusion in two to four divided doses [49]. One million international units of CMS is approximately equivalent to 30 mg CBA and 80 mg CMS. Because the two possible ways of expressing a colistin dose in milligrams (ie, as milligrams of CBA or as milligrams of CMS) can lead to medication errors that threaten patient safety, the Prato polymyxin consensus suggests that the expression of dose as milligrams of CMS in the dose section of product information should cease [50]. The daily dose of CMS should not exceed 9 million units (Europe) or 300 mg (5 mg/kg) of CBA (United States). Colistimethate 30–60 mg of CBA can be used by aerosol inhalation two times a day to treat pulmonary infections caused by XDR bacteria. A supply of at least one of polymyxins (colistin or polymyxin B) should be maintained as last-line antibiotics for the treatment of XDR bacterial infections in countries where the products are not currently registered, such as China.

**Quinolones.** Quinolone antibiotics have good antimicrobial activity against *P. aeruginosa* and *S. maltophilia*. Newer quinolone antibacterials such as moxifloxacin are more active against *S. maltophilia* than ciprofloxacin and levofloxacin [45,51]. In 2014, 12.9% and 8.25% of the *P. aeruginosa* and *S. maltophilia* isolates were resistant to ciprofloxacin, respectively [14]. Quinolones can be used in combination with β-lactams, aminoglycosides or polymyxins for treatment of the infections caused by XDR *P. aeruginosa* [52] or *S. maltophilia* [45,51]. The daily dose of ciprofloxacin is generally 0.6–1.2 g for adults in two to three divided oral doses. The recommended dose of levofloxacin for adults is usually 0.5 or 0.75 g once daily by oral or intravenous infusion. The recommended dose of moxifloxacin for adults is 400 mg intravenous infusion once daily.

**Sulbactam and sulbactam-containing combinations.** The β-lactamase inhibitor sulbactam is active against *Acinetobacter* spp. Thus, sulbactam-based fixed-dose combinations have shown good antimicrobial activity for *Acinetobacter* strains. Ampicillin–sulbactam is usually used in many countries, but cefoperazone–sulbactam is used more frequently to treat MDR *A. baumannii* infections in China, as the latter shows lower resistance rates than the former (12% vs. 34%) [53]. In general, the recommended upper limit of the sulbactam dose is 4.0 g/day, but it can be increased to 6.0 g/day or even 8.0 g/day for MDR and XDR *A. baumannii* infections [49]. The dose should be adjusted for patients with reduced renal function. It can be combined with other antimicrobial agents such as carbapenems [54] to treat infections caused by XDR *A. baumannii*.

**Cefoperazone–sulbactam.** The usual dosing regimen is 3.0 g (cefoperazone 2.0 g plus sulbactam 1.0 g) intravenous infusion every 8 hours or every 6 hours. Cefoperazone–sulbactam is usually used in combination with tigecycline, minocycline [55,56], carbapenems or aminoglycosides to treat XDR *A. baumannii* infections in China.

**Tetracyclines.** Minocycline is one of the few recommended antimicrobial agents for treating *S. maltophilia* infections. The US FDA has approved minocycline injection for treatment of *A. baumannii* infections. The dosing regimen of minocycline is 100 mg intravenous infusion every 12 hours. Clinical data are lacking in this respect. Currently minocycline injection is not available in China. Minocycline tablets or doxycycline injection (an equivalent dose of minocycline) can be used in combination with other antimicrobial agents for the treatment of infections caused by XDR *A. baumannii* [42,55,56] or *S. maltophilia* [45,46,51].

**Tigecycline.** As the first antibiotic of glycylcyclines, it remains active for CRE and XDR *A. baumannii*. Tigecycline susceptibility rates are 98% and 90% for carbapenem-resistant Klebsiella spp. and *Acinetobacter* spp., respectively; 92% of the *S. maltophilia* isolates are susceptible to tigecycline [57]. Recent reports on the susceptibility of *A. baumannii* to tigecycline vary greatly [58]. Therefore, it should be used according to the results of susceptibility testing. Tigecycline is inactive against *P. aeruginosa*. Tigecycline is distributed extensively in body tissues and is associated with low blood concentration [19]. It is therefore
inappropriate to use tigecycline alone for managing bloodstream infection. Since its launch in China in 2012, tigecycline has been used primarily to treat the respiratory tract, skin and soft tissue, and abdominal infections caused by XDR A. baumannii or Enterobacteriaceae. It is usually used in combination with cefoperazone–sulbactam, carbapenems or aminoglycosides. Tigecycline is also used in combination with polymyxin [59]. Clinical data are still lacking for tigecycline in the treatment of S. maltophilia infections [45,51]. The usual dosing regimen of tigecycline is 100 mg, followed by 50 mg every 12 hours by intravenous infusion. Preliminary studies indicate that increasing the tigecycline dose may improve its efficacy in treating severe bacterial infections, especially complicated intra-abdominal infection [60], hospital-acquired pneumonia (HAP) [61] and VAP (Ventilator-associated pneumonia) [62]. However, this finding requires confirmation. The main adverse reactions of tigecycline are gastrointestinal reactions.

**Trimethoprim–sulphamethoxazole (TMP-SMX).** TMP-SMX has good antimicrobial activity against S. maltophilia, with resistance rates lower than 10% [14,44,45]. Approximately 87% of the MDR S. maltophilia strains are still susceptible to this drug. TMP-SMX combined with minocycline or ceftazidime has shown good in vitro antimicrobial activity (partially synergistic) against MDR S. maltophilia strains [46]. TMP-SMX is the first choice for treating S. maltophilia infections [45,51]. TMP-SMX is also active against a few XDR A. baumannii and CRE strains.

Others. Rifampicin has shown certain antimicrobial activity against A. baumannii. It can be used in combination with carbapenems for treatment of the infections caused by XDR A. baumannii [63]. However, a recent randomized clinical trial indicated that 30-day mortality is not reduced by addition of rifampicin to colistin in serious XDR A. baumannii infections [64]. A few XDR-GNB strains including NDM-1-producing Enterobacteriaceae strains are susceptible to aztreonam [65], which might be used in combination therapy for such strains.

**New antimicrobial agents.** Two β-lactamase inhibitor combinations, ceftazidime–avibactam and cefotaxime–tazobactam, have been approved by the US FDA for the treatment of complicated intra-abdominal infections and complicated urinary tract infections in the United States in February 2015 and December 2014, respectively. Avibactam is a synthetic non-β-lactam β-lactamase inhibitor that inhibits the activities of Ambler class A (including extended-spectrum β-lactamase), class C (especially AmpC) and class D (such as OXA-48) β-lactamases as well as KPC carbapenemases. The addition of avibactam greatly improves the activity of ceftazidime versus most species of Enterobacteriaceae and P. aeruginosa as well. Limited data suggest that the addition of avibactam does not improve the activity of ceftazidime versus Acinetobacter species [66]. A randomized active-controlled, double-blind, phase 2 trial proved that ceftazidime–avibactam plus metronidazole was as effective and well tolerated in patients with complicated intra-abdominal infections as meropenem [67].

Ceftolozane is a novel cephalosporin with a structure similar to ceftazidime that is distinguished from other cephalosporins by improved activity against P. aeruginosa, including various drug-resistant phenotypes such as carbapenem-, piperacillin–tazobactam- and ceftazidime-resistant isolates, as well as strains that are MDR isolates [68]. Phase 2 and phase 3 clinical trials of ceftolozane–tazobactam have been completed. In a phase 2 trial, ceftolozane–tazobactam plus metronidazole resulted in similar clinical and microbiologic success rates as meropenem in the treatment of complicated intra-abdominal infections [69].

**Control of XDR-GNB hospital infections**

The increase of XDR-GNB infections results from the combined effect of antibiotic selection pressure and spread of resistant clones. Infection control measures must be appropriately integrated with antimicrobial stewardship to effectively curb and prevent the spread of XDR-GNB, and to reduce infections caused by resistant bacteria [19,70,71].

**Hand hygiene**

Hand hygiene is the most fundamental, effective and cost-effective strategy for reducing cross-infections and avoiding the spread of resistant bacteria through the hands of healthcare staff [71].

**Contact precaution**

The microbiology laboratory should notify clinicians in a timely and reliable way when an XDR-GNB strain is identified. Clinicians may implement contact precaution measures such as single room and partial separation of at least 1 m between beds for patients infected with XDR-GNB and to reduce the practice of sharing devices. Sphygmomanometer, stethoscope, thermometer, infusion pump and other relevant devices should be provided specifically for patients with XDR-GNB infection [70]. When a patient infected with XDR-GNB is transferred to another department or hospital, or leaves the ward for examination, handover procedures and warning tips are required [72].

**Active screening**

In the ICU and other wards with highly prevalent XDR-GNB strains, patients should be screened with samples of perianal and rectal swabs for CRE, wound secretion and nasopharyngeal region for XDR nonfermenters to promptly identify resistant
bacteria by way of conventional or rapid diagnostic methods [71]. The patients should be isolated appropriately. Molecular epidemiologic measures may be adopted to track the route of transmission if necessary to provide a rationale for blocking transmission of resistant bacteria [73].

Environmental surface disinfection

The surface of the objects frequently contacted by healthcare staff and patients in the hospital environment should be disinfected regularly and completely [71,74]. Fluorescence labeling or the ATP Hygiene Monitoring System can be used to monitor the effectiveness of disinfection and thus ensure that the transmission of resistant strains is effectively blocked.

Decolonization

Patients colonized with XDR-GNB may have a whole-body sponge bath with chlorhexidine, which is helpful for reducing catheter-related bloodstream infections [75].

Management of antimicrobial agent use in the clinical setting

We recommend strictly adhering to indications for the clinical use of antimicrobial agents; limiting antimicrobial use through restriction of specific agents (e.g. carbapenems, tigecycline and polymyxin); and formulating evidence-based treatment guidelines or dosing regimens according to the local profile of resistant bacteria to guide and standardize the use of antimicrobial agents.

A rational and appropriate formulary should be developed to ensure the supply of antimicrobial agents necessary for clinical treatment, including newer antimicrobial agents. Available evidence for the effects of antimicrobial rotation or cycling on curbing increasing antimicrobial resistance is contradictory [76]. Furthermore, in hospitals or specific wards with highly prevalent XDR-GNB, some GNB species are highly resistant to nearly all antimicrobial agents available. Therefore, caution must be exercised when considering exclusion of a specific category of antimicrobial agents in a medical institution or in specific wards.

Transparency declaration

All authors report no conflicts of interest relevant to this article.

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