ORIGINAL ARTICLE

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.

Keywords: *Enterobacteriaceae* infection, multidrug resistant (MDR), pandrug resistant (PDR), XDR, XDR *Acinetobacter* infection, XDR *Pseudomonas aeruginosa* infection
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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), $\leq$16/8 mg/L; intermediate (I), 32/16 mg/L; and resistant (R), $\geq$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