Multi-Drug Resistance

Subjects: Microbiology | Others
Contributor: Emanuele Palomba

Multidrug-resistance is a long debated term. Since 1980 it was used to imply the resistance of a microorganism to multiple pharmaceutical agents, without the number or types of antimicrobials being specified.
Currently, the most widely accepted definition of multidrug-resistant (MDR) bacteria include a lack of susceptibility in three or more antimicrobial categories active against the isolated microorganism.

Keywords: multidrug-resistant ; MDR ; XDR ; PDR ; antimicrobial resistance ; extensively drug-resistant ; pandrug-resistant

1. Current definition

Multidrug-resistance is a long debated term. Since 1980 it was used to imply the resistance of a microorganism to multiple pharmaceutical agents, without the number or types of antimicrobials being specified.

In 2011 a group of international experts came together through a joint initiative by the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC), to create a standardized international terminology with which to describe acquired resistance profiles in *Staphylococcus aureus*, *Enterococcus* spp., Enterobacterales (other than *Salmonella* and *Shigella*), *Pseudomonas aeruginosa* and *Acinetobacter* spp. [1] In order to assess antimicrobial susceptibility within different groups of pathogens, lists of antimicrobial categories (Table 1-5) were created using documents and breakpoints from the Clinical Laboratory Standards Institute (CLSI), the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the United States Food and Drug Administration (FDA).

The ECDC-CDC consensus proposed the following definitions for the characterization of bacterial isolates:

- MDR: multidrug-resistant, non-susceptibility to at least 1 agent in ≥ 3 antimicrobial categories
- XDR: extensively drug-resistant, non-susceptibility to at least 1 agent in all but 2 or fewer antimicrobial categories
- PDR: pandrug-resistant, non-susceptibility to all agents in all categories

When a species had intrinsic resistance to an antimicrobial category, that category was removed from the list prior to applying the criteria for the definitions and wasn't counted when calculating the number of categories to which the bacterial isolate was non-susceptible.

Within the definition of MDR, a unique rule was applied defining antibiotic resistance for methicillin resistant *S. aureus* (MRSA): finding an isolate resistant to oxacillin or cefoxitin predicts non-susceptibility to all categories of β-lactamase inhibitors and carbapenems, hence a MRSA will always be characterized as MDR.

Table 1. Antimicrobial categories tested for *S. aureus*.

Antimicrobial category	Antimicrobial agent
Aminoglycosides	Gentamicin
Ansamycins	Rifampin/rifampicin

Anti-MRSA cephalosporins	Ceftaroline
Anti-staphylococcal β-lactams (or cephamycins)	Oxacillin (or cefoxitin)a
Fluoroquinolones	Ciprofloxacin Moxifloxacin
Folate pathway inhibitors	Trimethoprim-sulphamethoxazole
Fucidanes	Fusidic acid
Glycopeptides	Vancomycin Teicoplanin Telavancin
Glycylcyclines	Tigecycline
Lincosamides	Clindamycin
Lipopeptides	Daptomycin
Macrolides	Erythromycin
Oxazolidinones	Linezolid
Phenicols	Chloramphenicol
Phosphonic acids	Fosfomycin
Streptogramins	Quinupristin-dalfopristin
Tetracyclines	Tetracycline Doxycycline Minocycline

Table 2. Antimicrobial categories tested for *Enterococcus* spp.

Antimicrobial category	Antimicrobial agent	Species with intrinsic resistance to antimicrobial categories
Aminoglycosides (except streptomycin)	Gentamicin (high level)	
Streptomycin	Streptomycin (high level)	
Carbapenems	Imipenem Meropenem Doripenem	*Enterococcus faecium*
Fluoroquinolones	Ciprofloxacin Levofloxacin Moxifloxacin	
Glycopeptides	Vancomycin Teicoplanin	
Glycylcyclines	Tigecycline	
Lipopeptides	Daptomycin	
Oxazolidinones	Linezolid	
Penicillins	Ampicillin	
Streptogramins	Quinupristin-dalfopristin	*Enterococcus faecalis*
Tetracycline	Doxycycline Minocycline	

Table 3. Antimicrobial categories tested for Enterobacterales.

Antimicrobial category	Antimicrobial agent	Species with intrinsic resistance to antimicrobial agents or categories
Aminoglycosides	Gentamicin	*Providencia rettgeri* (*P. rettgeri*), *Providencia stuartii* (*P. stuartii*)
	Tobramycin	*P. rettgeri, P. stuartii*
	Amikacin	
	Netilmicin	*P. rettgeri, P. stuartii*
Anti-MRSA cephalosporins	Ceftaroline (approved only for *Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca*)	
Antipseudomonal penicillins + *β*-lactamase inhibitors	Ticarcillin-clavulanic acid	*Escherichia hermannii* (*E. hermanii*)
	Piperacillin-tazobactam	*E. hermanii*
Carbapenems	Ertapenem	
	Imipenem	
	Meropenem	
	Doripenem	
Non-extended spectrum cephalosporins; 1st and 2nd generation cephalosporins	Cefazolin	*Citrobacter freundii* (*C. freundii*), *Enterobacter aerogenes* (*E. aerogenes*), *Enterobacter cloacae* (*E. cloacae*), *Hafnia alvei* (*H. alvei*), *Morganella morganii* (*M. morganii*), *Proteus penneri* (*P. penneri*), *Proteus vulgaris* (*P. vulgaris*), *P. rettgeri, P. stuartii, Serratia marcescens* (*S. marcescens*)
	Cefuroxime	*M. morganii, P. penneri, P. vulgaris, S. marcescens*
Extended-spectrum cephalosporins; 3rd and 4th generation cephalosporins	Cefotaxime or ceftriaxone	
	Ceftazidime	
	Cefepime	
Cephamycins	Cefoxitin	*C. freundii, E. aerogenes, E. cloacae, H. alvei*
	Cefotetan	*C. freundii, E. aerogenes, E. cloacae, H. alvei*
Fluoroquinolones	Ciprofloxacin	

Antimicrobial category	Antimicrobial agent	Species with intrinsic resistance to antimicrobial agents or categories
Folate pathway inhibitors	Trimethoprim-sulphamethoxazole	
Glycylcyclines	Tigecycline	*M. morganii, Proteus mirabilis* (*P. mirabilis*), *P. penneri, P. vulgaris, P. rettgeri, P. stuartii*
Monobactams	Aztreonam	
Penicillins	Ampicillin	*Citrobacter koseri* (*C. koseri*), *C. freundii, E. aerogenes, E. cloacae, E. hermanii, H. alvei, Klebsiellae spp., M. morganii, P. penneri, P. vulgaris, P. rettgeri, P. stuartii, S. marcescens*
Penicillins + *β*-lactamase inhibitors	Amoxicillin-clavulanic acid	*C. freundii, E. aerogenes, E. cloacae, H. alvei, M. morganii, P. rettgeri, P. stuartii, S. marcescens*
	Ampicillin-sulbactam	*C. freundii, C. koseri, E. aerogenes, E. cloacae, H. alvei, P. rettgeri, S. marcescens*
Phenicols	Chloramphenicol	
Phosphonic acids	Fosfomycin	
Polymyxins	Colistin	*M. morganii, P. mirabilis, P. penneri, P. vulgaris, P. rettgeri, P. stuartii, S. marcescens*
Tetracyclines	Tetracycline	*M. morganii, P. mirabilis, P. penneri, P. vulgaris, P. rettgeri, P. stuartii*
	Doxycycline	*M. morganii, P. penneri, P. vulgaris, P. rettgeri, P. stuartii*
	Minocycline	*M. morganii, P. penneri, P. vulgaris, P. rettgeri, P. stuartii*

Table 4. Antimicrobial categories tested for *P. aeruginosa.*

Antimicrobial category	Antimicrobial agent
Aminoglycosides	Gentamicin
	Tobramycin
	Amikacin
	Netilmicin

	Imipenem
Antipseudomonal carbapenems	Meropenem
	Doripenem
	Ceftazidime
Antipseudomonal cephalosporins	
	Cefepime
	Ciprofloxacin
Antipseudomonal fluoroquinolones	
	Levofloxacin
	Ticarcillin-clavulanic acid
Antipseudomonal penicillins + β-lactamase inhibitors	
	Piperacillin-tazobactam
Monobactams	Aztreonam
Phosphonic acids	Fosfomycin
	Colistin
Polymyxins	
	Polymyxin B

Table 5. Antimicrobial categories tested for *Acinetobacter spp.*

Antimicrobial category	**Antimicrobial agent**
	Gentamicin
	Tobramycin
Aminoglycosides	
	Amikacin
	Netilmicin
	Imipenem
Antipseudomonal carbapenems	Meropenem
	Doripenem
	Ciprofloxacin
Antipseudomonal fluoroquinolones	
	Levofloxacin

Antimicrobial category	Antimicrobial agent
Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam
	Ticarcillin-clavulanic acid
Extended-spectrum cephalosporins	Cefotaxime
	Ceftriaxone
	Ceftazidime
	Cefepime
Folate pathway inhibitors	Trimethoprim-sulphamethoxazole
Penicillins + β-lactamase inhibitors	Ampicillin-sulbactam
Polymyxins	Colistin
	Polymyxin B
Tetracyclines	Tetracycline
	Doxycycline
	Minocycline

2. Epidemiology of MDR bacteria

2.1 European data

European Antimicrobial Resistance Surveillance Network (EARS-Net) collects data on invasive isolates (blood and cerebrospinal fluid) from 30 countries (all EU member and two EEA countries).

Results on antimicrobial resistance are elaborated determining a population-weighted EU/EEA mean percentage and the temporal trends in resistance percentages by country is calculated based on data from the last four years. Several factors may influence the estimates and may results in over as well as underestimation of resistance percentages, nevertheless more than half countries reported a population coverage of 80% or higher.

Data from EARS-Net 2018 report[2], stated that more than half (58.3%) of the Escherichia coli isolates responsible for invasive diseases were resistant to at least one of the antimicrobial groups unde regular surveillance. The highest population-weighted mean resistance percentage was reported for aminopenicillins (57.4%), followed by fluoroquinolones (25.3%), third-generation cephalosporins (15.1%), and aminoglycosides (11.1%), with a significant increasing trend. On the contrary, E. coli resistance to carbapenems remains rare in Europe, ranging from 0 to 2%. Italy is one of the European countries with the highest percentage of antimicrobial resistance: in 2017, 41.7% of E. coli isolated from blood and cerebrospinal fluid were resistant to fluoroquinolones, and 28.7% were resistant to third-generation cephalosporins.

Likewise E. coli, Klebsiella pneumoniae can also be resistant to multiple antimicrobial agent. In the EARS-Net 2018 report, more than a third (37.2%) of all K. pneumoniae isolates that were resistant to at least one of the tested antimicrobial groups. The highest population-weighted mean resistance percentage was reported for third-generation cephalosporins (31.7%), followed by fluoroquinolones (31.6%), aminoglycosides (22.7%), and carbapenems (7.5%). Percentages of invasive isolates of carbapenem-resistant K. pneumoniae (CR-Kp) in Europe show a large variability,

ranging from 0 to 64.7%. The population-weighted mean percentage varied between 2014 and 2017, and was 7.3% in 2014 and 7.2% in 2017. In Italy, 53.6% of K. pneumoniae invasive isolates were resistant to third-generation cephalosporins and 26.8% to carbapenems.

Regarding P. aeruginosa, data from 2018 stated that 32.1% of the isolates were resistant to at least one of the antimicrobial groups under regular surveillance (see Table 4). The highest population-weighted mean resistance percentage in 2018 was reported for fluoroquinolones (19.7%), followed by piperacillin ± tazobactam (18.3%), carbapenems (17.2%), ceftazidime (14.1%) and aminoglycosides (11.8%). There were significantly decreasing trends in the population-weighted mean percentages of piperacillin ± tazobactam resistance, ceftazidime resistance, aminoglycoside resistance and carbapenem resistance between 2015 and 2018. By excluding all laboratories apart from those that consistently reported data for all four years, only the decreasing trends for aminoglycoside resistance and carbapenem resistance remained statistically significant. Resistance to two or more antimicrobial groups was common and seen in 19.2% of all tested isolates. The population-weighted mean percentage of combined resistance, defined as resistance to at least three of the antimicrobial groups under surveillance, significantly decreased between 2015 and 2018. Large inter-country variations were seen for all antimicrobial groups, with generally higher resistance percentages reported from southern and eastern Europe than northern Europe

More than half of the Acinetobacter species isolates reported by European countries (56.4%) were resistant to at least one of the antimicrobial groups under regular surveillance (i.e. fluoroquinolones, aminoglycosides and carbapenems). The highest population-weighted mean resistance percentage in 2018 was reported for fluoroquinolones (36.2%), followed by aminoglycosides (31.9%) and carbapenems (31.9%). Resistance to one or two antimicrobial groups was considerably less common than combined resistance to all three groups under surveillance. In 2018, the population-weighted mean percentage for combined resistance to fluoroquinolones, aminoglycosides and carbapenems was 28.8%. Large inter-country variations were noted for all antimicrobial groups under regular surveillance, with generally higher resistance percentages reported from southern and eastern Europe than from northern Europe. Single resistance to one antimicrobial group was less common in countries reporting comparatively low proportions of fully susceptible isolates.

The population-weighted mean percentage of MRSA was 16.4% in 2018. This is a result of a significantly decreasing trend between 2015 and 2018. In 2018, large differences in national MRSA percentages were noted, ranging from 0% to 43.0% . Close to a third of the countries reported significantly decreasing trends during the period 2015–2018, including countries with both low and high percentages of MRSA. Among MRSA, combined resistance to other antimicrobial groups was common. The most common resistance combination was MRSA and resistance to fluoroquinolones. Rifampicin resistance was less common.

In 2018, the population-weighted mean percentage of high-level gentamicin resistance in E. faecalis was 27.1%, with national percentages ranging from 6.7% to 41.6%. The European trend decreased significantly between 2015 and 2018, with similar significantly decreasing national trends reported from almost one quarter of the countries. Vancomycin resistance in E. faecalis remained low in most countries.

The European population-weighted mean percentage of vancomycin resistance in E. faecium was 17.3%, which represents a significant increase from 2015 when the percentage was 10.5%. National percentages ranged from 0.0% to 59.1%. Only 12 of the 30 reporting countries reported resistance percentages below 5%. Several of the countries reporting comparatively high percentages of resistance to vancomycin also reported significantly increasing trends for the last four years. For several countries, the increase during the four-year period was considerable. With few exceptions, national percentages of high-level aminoglycoside resistance in E. faecium were higher than for E. faecalis.

2.2. United States Data

The 2019 CDC's *Antibiotic Resistance Threats in the United States,* reporting data regarding the year 2017, states that more than 2.8 million antibiotic-resistant infections occur in the U.S. each year, and more than 35000 people die as a result.[3]

According to the report, in 2017 there were 13100 cases of infections caused by carbapenem-resistant Enterobacterales were reported, showing a slow but steady increasing trend since 2012. Moreover, extended-spectrum beta-lactamase (ESBL) producing Enterobacterales were isolated in 197400 cases in hospitalized patients. Within the same year MDR P. aeruginosa infections caused 2700 estimated deaths and 32600 cases in hospitalized patients.
Regarding carbapenem-resistant *Acinetobacter* spp, there were 8500 estimated cases of infection in hospitalized patients, with 89% of the isolates non-susceptible to any fluoroquinolones, 75% to any extended-spectrum β-lactam, 61% to ampicillin-sulbactam and 66% of the isolates non-susceptible to trimethoprim-sulfamethoxazole (TMP-SMX).

Vancomycin-resistant enterococci accounted for 54500 cases, with 30% of all healthcare-associated enterococcals infections showing non-susceptibility to vancomycin.
Estimated cases of MRSA infections showed a constant reduction between 2005 and 2017, with 323700 cases and 10600 estimated deaths, with approximately 5% of patients in U.S. hospitals carrying MRSA in their nose or on their skin.

3. Future perspectives

The ECDC/ CDC definition of multidrug-resistance, based on the criteria used for tuberculosis, can prove to be impractical[4]. Firstly, finding a universal consensus is difficult to achieve, since not all antimicrobials are available and tested by laboratories in all countries, and there is no common testing policy for laboratories. Furthermore, differences between European (EUCAST) and US (CLSI or FDA) breakpoints can affect fundamentally whether isolates are regarded as MDR or XDR. Secondly, some antibiotic resistances are now very common and stable, so they are seldom tested for, but if they are present the organism needs only one further resistance to count as MDR according to the “three classes of resistance” rule. Lastly, assigning antibiotics to separate classes without considering resistance mechanisms can lead to further discussion, making it difficult to reach a shared consensus.

More viable definitions for MDR bacteria are needed. Lack of universal agreement influences recruitment and classification of patients in clinical trials and hampers effective surveillance of MDR strains. A useful pragmatic approach to defining MDR can be to consider oral and parenteral drugs separately. For oral drugs, multi-resistance can be defined as a microorganism susceptible to only one or no readily available oral agent active against infections systemically or in the upper urinary tract. For parenteral antibiotics a similar approach can be considered. Specific agents to which impaired susceptibility might be significant include carbapenems, relevant cephalosporins (cefotaxime for Enterobacterales, ceftazidime for *P. aeruginosa*), aztreonam, ceftolozane/tazobactam, ceftazidime/avibactam, temocillin, piperacillin/tazobactam, colistin, quinolones, fosfomycin, tigecycline and aminoglycosides (including amikacin).

References

1. A-P Magiorakos , A Srinivasan, R B Carey, Y Carmeli, M E Falagas, C G Giske, S Harbarth, J F Hindler, G Kahlmeter, B Olsson-Liljequist, D L Paterson, L B Rice, J Stelling, M J Struelens, A Vatopoulos, J T Weber, D L Monnet; Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect .* **2011**, *18(3)*, 268-81, .
2. Surveillance of Antimicrobial Resistance in Europe . ECDC. Retrieved 2020-8-13
3. 2019 CDC’s Antibiotic Resistance Threats in the United States . CDC. Retrieved 2020-8-13
4. Hawkey, Peter; Warren, Roderic E; Livermore, David M; McNulty, Cliodna A M; Enoch, David A; Otter, Jonathan A; Wilson, Peter R; Treatment of infections caused by multidrug-resistant Gram-negative bacteria: report of the British Society for Antimicrobial Chemotherapy/Healthcare Infection Society/British Infection Association Joint Working Party. *J Antimicrob Chemother* **2018**, *Mar 1;73(suppl_3)*, iii2-iii78, 10.1093/jac/dky027.