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ORIGINAL ARTICLE

A global priority list of the TOp TEn resistant Microorganisms (TOTEM) study at intensive care: a prioritization exercise based on multi-criteria decision analysis

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Abstract

The World Health Organization (WHO) proposed a global priority pathogen list (PPL) of multidrug-resistant (MDR) bacteria. Our current objective was to provide global expert ranking of the most serious MDR bacteria present at intensive care units (ICU) that have become a threat in clinical practice. A proposal addressing a PPL for ICU, arising from the WHO Global PPL, was developed. Based on the supporting data, the pathogens were grouped in three priority tiers: critical, high, and medium. A multi-criteria decision analysis (MCDA) was used to identify the priority tiers. After MCDA, mortality, treatability, and cost of therapy were of highest concern (scores of 19/20, 19/20, and 15/20, respectively) while dealing with PPL, followed by healthcare burden and resistance prevalence. Carbapenem-resistant (CR) *Acinetobacter baumannii*, carbapenemase-expressing *Klebsiella pneumoniae* (KPC), and MDR *Pseudomonas aeruginosa* were identified as critical organisms. High-risk organisms were represented by CR *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, and extended-spectrum beta-lactamase (ESBL) *Enterobacteriaceae*. Finally, ESBL *Serratia marcescens*, vancomycin-resistant *Enterococci*, and TMP-SMX-resistant *Stenotrophomonas maltophilia* were identified as medium priority. We conclude that education, investigation, funding, and development of new antimicrobials for ICU organisms should focus on carbapenem-resistant Gram-negative organisms.

Keywords Multidrug-resistant bacteria · Infection control · Colonization · Prevention · Research · Antimicrobials · Intensive care · Sepsis

Introduction

Multidrug-resistant (MDR) bacteria have become a health priority [1] and efforts have been made to prevent colonization, infection, and decrease mortality [2–7]. The World Health Organization (WHO) proposed a global priority pathogen list (PPL) of MDR bacteria to guide research, discovery, and development of new antibiotics [3, 8]. However, critically ill

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patients are particularly susceptible to infections arising from MDR bacteria [9, 10]. To develop a more solid understanding of the issues facing critically ill patients, we established the TOp TEn resistant Microorganisms (TOTEM) in critical care study group (Appendix 1). The scope was to identify the most important resistant bacteria for intensive care units (ICU) for which there is an urgent need for new therapies. The primary objective of the TOTEM study was to describe, as assessed by expert opinion and current evidence, a global list of the top ten most clinically relevant MDR bacteria affecting critically ill patients. The secondary objective was to prioritize the list to focus efforts proportionately according to perceived clinical need.

Methods

The study consisted of score prioritization by a panel of ten experts invited to prioritize organisms using MCDA. A steering committee (Appendix 2a) with experience of identification, prevention, and treatment of MDR bacteria in critically ill patients were invited to participate. They contributed in the revision of first drafts of the study protocol and selection of pathogens. *Mycobacteria*, *Rickettsia*, viruses, and parasites were excluded. Panel experts were suggested by the TOTEM project leader (JR) based on their prior experience or their expertise in clinical practice, clinical trials, and publications, seeking to provide global geographic coverage and membership from the range of professionals whose roles are impacted by MDR bacteria. MDR bacteria were defined as reported elsewhere [6]. The coordinating group represented intensivists, anesthesiologists, clinical microbiologists, and infectious disease (ID) consultants with experience in ICU settings (Appendix 2b). Pediatric and neonatal intensive care units (ICUs) were excluded. The list was ranked using the following (WHO) prioritization factors: all-cause mortality, healthcare and community burden, prevalence of resistance, 5-year trend of resistance, transmissibility and preventability, treatability, and current drug pipeline, with the addition of estimated cost of therapy. Definitions for the variables used in the prioritization list were reported elsewhere [8]. For each variable, scores were assigned from 1 (least) to 10 (most) according to importance and the average value was multiplied by 2 providing a maximal potential score of 20. The study used no patient-specific data and thus the need for ethical research committee approval or informed consent was waived.

Statistical and MCDA analysis

All responses were categorical variables presented as summary statistics, reporting proportions (percentages). The prioritization exercise was performed through the following steps: (1) selection of antibiotic-resistant organisms to be prioritized, (2) selection for criteria of prioritization, (3) data extraction and synthesis, (4) scoring of the alternatives and weighting of criteria by experts, and (5) finalization of the pathogens' ranking. As a summary of sources of data on the different variables, participants were referred to the evidence-based information released by the WHO final report [8]. Data sources were PubMed and Ovid databases and did not have time restriction, last update in September 2016. The multiple-criteria decision analysis (MCDA) methodology has been detailed in Online Resource 1.

Results

After MCDA, mortality and treatability were of highest concern (Scores of 19/20) while dealing with PPL, followed by cost of treatment, healthcare burden, and resistance prevalence. Carbapenem-resistant (CR) *Acinetobacter baumannii*, *Klebsiella pneumoniae*-expressing carbapenemase (KPC), and MDR *Pseudomonas aeruginosa* were classified as critical organisms. High-risk organisms were represented by CR *P. aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA), and extended-spectrum beta-lactamase (ESBL) Enterobacteriaceae. Finally, ESBL *Serratia marcescens*, vancomycin-resistant E*nterococci*, and TMP-SMX-resistant *Stenothophomonas maltophilia* were identified as medium priority. Distribution of scores is detailed in Table 1. In the PPL scoring, CR *A. baumannii*, KPC, and MDR *P. aeruginosa* scored high for mortality, treatability, and cost of treatment while MDR *P. aeruginosa*, KPC, and ESBL *K.pneumoniae* were prioritized for healthcare burden. Overall prevalence of resistance was high for ESBL Enterobacteriaceae. Along with other critical and high-priority pathogens, *S. marcescens* too scored high among difficult to treat pathogens. Preventability was worst with KPC followed by MRSA.

Discussion

CR *Acinetobacter baumannii*, CR *Klebsiella pneumoniae*, and MDR *Pseudomonas aeruginosa* were classified as critical organisms (priority 1), confirming the WHO PPL [8]. In contrast, priority 2 represented by high-risk organism is markedly different. However, this finding is not a surprise as the risk factors for the selection of resistant organisms in hospitals vary from the community. Our findings emphasize a global concern regarding Gram-negative bacteria.

Indeed, while dealing with PPL, mortality and treatability were considered the highest priority followed by cost of treatment, healthcare burden, and resistance prevalence in MCDA

Table 1 Weighting of the criteria and the scores for the priority list of resistant microorganisms at intensive care units

Pathogen list	Rank order of criteria (mean score)										Priority level
	Mortality (19)	Treatability (19)	Cost of treatment (15)	Health care burden (13)	Prevalence of resistance (12)	Preventability (10)	Transmissibility (7)	Current pipeline (7)	Community burden (5)	Sum score	
Carbapenem-resistant *A. baumannii*	144.88	137.75	112.50	87.75	67.50	60.00	52.50	47.25	26.25	736.38	Critical
Carbapenemase expressing-*K.pneumoniae* (KPC)	147.25	130.63	114.38	92.63	52.50	77.50	29.75	47.25	24.29	716.16	
Multidrug-resistant *P. aeruginosa*	147.25	125.88	110.63	95.88	70.50	57.50	44.63	32.38	25.71	710.34	
Carbapenem-resistant *P. aeruginosa*	144.88	125.88	116.25	68.25	57.00	58.75	33.25	52.50	18.75	675.50	High
Extended-spectrum beta-lactamase *K. pneumoniae*	102.13	114.00	63.75	91.00	88.50	56.25	38.50	42.88	42.50	639.50	
Methicillin-resistant *S. aureus* (MRSA)	116.38	85.50	80.63	79.63	84.00	67.50	48.13	39.38	33.13	634.25	
Extended-spectrum beta-lactamase *E. coli*	76.00	90.25	71.25	81.25	97.50	58.75	42.00	42.00	48.75	607.75	
Vancomycin-resistant *Enterococci* (VRE)	64.13	64.13	71.25	53.63	67.50	42.50	51.63	27.13	21.88	463.75	Medium
Extended-spectrum beta-lactamase *Serratia* spp	57.00	104.50	52.50	48.75	52.50	42.50	29.75	34.13	25.63	447.25	
TMP/SMX resistant *S.maltophilia*	45.13	73.63	41.25	16.25	24.00	28.75	14.88	20.13	12.50	276.50	

analysis. Carbapenem-resistant organisms were indisputably perceived as the highest threat for mortality, treatability, and cost. The results support the difficulty faced in managing MDR *P.aeruginosa* infections in ICUs [11]. Mortality by CR organisms is contributed particularly by the non-availability of effective drugs rather than increased virulence [12–15]. Currently, the biggest gap exists in the investigational pipeline for compounds active against CR *A. baumannii,* which is perceived as a critical organism for treatability. Our findings suggest that CR *A. baumannii* is of major concern, despite it being considered conventionally of low virulence [16]. Not surprisingly, given the focus on intensive care major concerns, the prioritization list came up with a different ranking of pathogens and resistance markers than the WHO PPL, which takes a more global view.

WHO reports estimate approximately 30% of ICU patients are affected by at healthcare-associated infections while incidence is 3-fold higher in low- and middle-income countries [17]. Several reports from these countries suggest the lack of surveillance data thus having a negative influence on the implementation of preventive measures [18–22]. Two EPIC studies in a span of 10 years have demonstrated a 20% increase in prevalence of ICU-acquired infections [23, 24].

There are a number of limitations to this study. The survey panel has not uniformly represented the regions of global hotspots of MDR infections, such as Asia, whereas Europe is over-represented. The study did not take into consideration the current evidence for infections in respect to the frequency and burden, discrepancies in CDC vs ECDC definitions, underlying immune status, sub-classification of infections based on underlying condition (medical, trauma, burns, cardiac surgery, special patient population etc), pediatric patients, and public health threats. Other bacterial pathogens causing severe infections that are potentially drug resistant and are acquired in the community were not covered. The strengths include the study methodology (MCDA) incorporating expert opinion and evidence-based data that showed a high stability of the final ranking and its future adaptability for regional updates of the priority pathogen lists.

Conclusions

Carbapenem-resistant *Acinetobacter baumannii*, carbapenemase-expressing *Klebsiella pneumoniae*, and MDR *Pseudomonas aeruginosa* were classified as critical organisms (priority 1) causing ICU infections. Education, investigation, funding, and development of new antimicrobials for ICU organisms should be focused on the identified priorities.

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Compliance with ethical standards

Competing interests Dr. Rello served in the speaker's bureau or consultant for Pfizer, Anchoagen, ROCHE. The remaining authors have no conflicts of interest to declare.

Ethical approval Not required.

Appendix 1. TOTEM Study Investigators

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Appendix 2a- Steering Committee members

Jordi Rello, Spain (Chair); Joana Alves, Portugal; Leonel Lagunes, Mexico; Jeroen Schouten, Netherlands; Celine Pulcini, France; Nieves Larrosa, Spain; Mervyn Mer, South Africa; Emine Alp, Turkey; Zhongheng Zhang, China.

Appendix 2b- Scoring Committee members

Emine Alp, Turkey; Andrew Conway-Morris, UK; Leonel Lagunes, Mexico; Davide Leoni, Italy; Jose Nicolas, Colombia; Jordi Rello, Spain, Vandana KE, India; Richard Wunderink, USA; Zhongheng Zhang, China.

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