Title page

Title: Global Priority List of TOp TEn resistant Microorganisms at Intensive Care (TOTEM study): A prioritization exercise based on multi-criteria decision analysis.

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Abstract

Purpose: The World Health Organization (WHO) proposed a global priority pathogen list (PPL) of multi-drug resistant (MDR) bacteria. Our current objective was to provide global expert ranking of the most serious multi-drug resistant (MDR) bacteria present at intensive care units (ICU) that have become a threat in clinical practice.

Methods: A proposal addressing a pathogens priority list (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 analyses (MCDA) was used to identify the priority tiers.

Results: After MCDA analysis, 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. Carbapenen-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.

Conclusions: 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.

Text

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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 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 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 was 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, 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 two 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. **Multiple-criteria decision analysis (MCDA) methodology has been detailed in Online Resource 1**

Results

After MCDA analysis, 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 priority pathogens list [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 highest priority followed by cost of treatment, healthcare burden and resistance prevalence in MCDA analysis. Carbapenem-resistant organisms were indisputably perceived as highest threat for mortality, treatability and cost. The results support the difficulty faced in managing MDR *P.aeruginosa* infections in ICUs [12]. Mortality by CR organisms is contributed particularly by the non-availability of effective drugs rather than increased virulence [13–16]. Currently, the biggest gap exists in the investigational pipeline for compounds active against CR *A. baumannii,* which is perceived as critical organism for treatability. Our findings suggest that CR *A. baumannii* is of major concern, despite it is considered conventionally low virulence [17]. 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 [18]. Several reports from these countries suggest the lack of surveillance data thus having a negative influence on the implementation of preventive measures [19–23]. Two EPIC studies in a span of 10 years have demonstrated 20% increase in prevalence of ICU-acquired infections [24,25].

There are a number of limitations to this study. The survey panel have 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), paediatric patients and public health threats. Other bacterial pathogens causing severe infections that are potentially drug resistant and are acquired at community were not covered. The strengths include the study methodology (MCDA) incorporating expert opinion and evidence based data that showed 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:

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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.

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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.

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	