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1 **Title page**

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

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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.

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Keywords

56 Multidrug-resistant bacteria, infection control, colonization, prevention, research, antimicrobials,

57 intensive care, sepsis.

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Text

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

83

84 **Introduction**

85 Multidrug resistant (MDR) bacteria have become a health priority [1] and efforts have been made to
86 prevent colonization, infection and decrease mortality [2–7]. The World Health Organization (WHO)
87 proposed a global priority pathogen list (PPL) of MDR bacteria to guide research, discovery and
88 development of new antibiotics [3, 8]. However, critically ill patients are particularly susceptible to
89 infections arising from MDR bacteria [9, 10]. To develop a more solid understanding of the issues
90 facing critically ill patients, we established the TOp TEn resistant Microorganisms (TOTEM) in critical
91 care study group (appendix 1). The scope was to identify the most important resistant bacteria for
92 intensive care units (ICU) for which there is an urgent need for new therapies. The primary objective
93 of the TOTEM study was to describe, as assessed by expert opinion and current evidence, a global list
94 of the top ten most clinically relevant MDR bacteria affecting critically ill patients. The secondary
95 objective was to prioritize the list to focus efforts proportionately according to perceived clinical need.

96 **Methods**

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

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116 **Statistical and MCDA analysis**

117 All responses were categorical variables presented as summary statistics, reporting proportions
118 (percentages). The prioritization exercise was performed through the following steps: 1. Selection of
119 antibiotic resistant organisms to be prioritized. 2. Selection for criteria of prioritization. 3. Data
120 extraction and synthesis. 4: Scoring of the alternatives and weighting of criteria by experts, and 5.

121 Finalization of the pathogens' ranking. As a summary of sources of data on the different variables,
122 participants were referred to the evidence-based information released by the WHO final report [8].
123 Data sources were PubMed and Ovid databases and did not have time restriction, last update in
124 September 2016. **Multiple-criteria decision analysis (MCDA) methodology has been detailed in**
125 **Online Resource 1**
126

127 **Results**

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

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145 **Discussion**

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

152 Indeed, while dealing with PPL, mortality and treatability were considered highest priority followed
153 by cost of treatment, healthcare burden and resistance prevalence in MCDA analysis. Carbapenem-
154 resistant organisms were indisputably perceived as highest threat for mortality, treatability and cost.
155 The results support the difficulty faced in managing MDR *P.aeruginosa* infections in ICUs [12].

156 Mortality by CR organisms is contributed particularly by the non-availability of effective drugs rather
157 than increased virulence [13–16]. Currently, the biggest gap exists in the investigational pipeline for
158 compounds active against CR *A. baumannii*, which is perceived as critical organism for treatability.

159 Our findings suggest that CR *A. baumannii* is of major concern, despite it is considered
160 conventionally low virulence [17]. Not surprisingly, given the focus on intensive care major concerns,
161 the prioritization list came up with a different ranking of pathogens and resistance markers than the
162 WHO PPL, which takes a more global view.

163

164 WHO reports estimate approximately 30% of ICU patients are affected by at healthcare-associated
165 infections while incidence is 3-fold higher in low and middle-income countries [18]. Several reports
166 from these countries suggest the lack of surveillance data thus having a negative influence on the
167 implementation of preventive measures [19–23]. Two EPIC studies in a span of 10 years have
168 demonstrated 20% increase in prevalence of ICU-acquired infections [24,25].

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

179 **Conclusions**

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

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211 **Competing Interests:** Dr Rello served in the speaker's bureau or consultant for Pfizer, Anchoagen,

212 ROCHE. The remaining authors have no conflicts of interest to declare.

213

214 **Ethical Approval:** Not required.

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322

323 **Appendix 2a- Steering Committee members**

324 Jordi Rello, Spain (Chair); Joana Alves, Portugal; Leonel Lagunes, Mexico; Jeroen Schouten,
325 Netherlands; Celine Pulcini, France; Nieves Larrosa, Spain; Mervyn Mer, South Africa; Emine Alp,
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327

328

329 **Appendix 2b- Scoring Committee members**

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331 Nicolas, Colombia; Jordi Rello, Spain, Vandana KE, India; Richard Wunderink, USA; Zhongheng Zhang,
332 China.

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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 <i>A. baumannii</i>	144.88	137.75	112.50	87.75	67.50	60.00	52.50	47.25	26.25	736.38	Critical
Carbapenemase expressing <i>K. pneumoniae</i> (KPC)	147.25	130.63	114.38	92.63	52.50	77.50	29.75	47.25	24.29	716.16	
Multidrug resistant <i>P. aeruginosa</i>	147.25	125.88	110.63	95.88	70.50	57.50	44.63	32.38	25.71	710.34	High
Carbapenem-resistant <i>P. aeruginosa</i>	144.88	125.88	116.25	68.25	57.00	58.75	33.25	52.50	18.75	675.50	
Extended-spectrum beta-lactamase <i>K. pneumoniae</i>	102.13	114.00	63.75	91.00	88.50	56.25	38.50	42.88	42.50	639.50	High
Methicillin-resistant <i>S. aureus</i> (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 <i>E. coli</i>	76.00	90.25	71.25	81.25	97.50	58.75	42.00	42.00	48.75	607.75	

Vancomycin resistant <i>Enterococci</i> (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 <i>Serratia</i> spp	57.00	104.50	52.50	48.75	52.50	42.50	29.75	34.13	25.63	447.25	
TMP/SMX resistant <i>S.maltophilia</i>	45.13	73.63	41.25	16.25	24.00	28.75	14.88	20.13	12.50	276.50	