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# A systematic literature review and expert consensus on risk factors associated to infection progression in adult patients with respiratory tract or rectal colonisation by carbapenem-resistant Gram-negative bacteria

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## ABSTRACT

**Objective.** Risk factors (RFs) associated with infection progression in patients already colonised by carbapenem-resistant Gram-negative bacteria (CRGNB) have been addressed in few and disperse works. The aim of this study is to identify the relevant RFs associated to infection progression in patients with respiratory tract or rectal colonisation.

**Material and methods.** A systematic literature review was developed to identify RFs associated with infection progression in patients with CRGNB respiratory tract or rectal colonisation. Identified RFs were then evaluated and discussed by the expert panel to identify those that are relevant according to the evidence and expert's experience.

**Results.** A total of 8 articles were included for the CRGNB respiratory tract colonisation and 21 for CRGNB rectal colonisation, identifying 19 RFs associated with pneumonia development and 44 RFs associated with infection progression, respectively. After discussion, the experts agreed on 13 RFs to be associated with pneumonia development after respiratory tract CRGNB colonisation and 33 RFs to be associated with infection progression after rectal CRGNB colonisation. Respiratory tract and rectal colonisation, previous stay in

the ICU and longer stay in the ICU were classified as relevant RF independently of the pathogen and site of colonisation. Previous exposure to antibiotic therapy or previous carbapenem use were also common relevant RF for patients with CRGNB respiratory tract and rectal colonisation.

**Conclusion.** The results of this study may contribute to the early identification of CRGNB colonized patients at higher risk of infection development, favouring time-to-effective therapy and improving health outcomes.

**Keywords:** Risk factor; Multi-drug resistance; Carbapenem-resistant gram-negative bacteria; colonization; expert consensus.

## Revisión sistemática de la literatura y consenso de expertos sobre los factores de riesgo asociados a la progresión de la infección en pacientes adultos con colonización del tracto respiratorio o rectal por bacterias gramnegativas resistentes a carbapenémicos

**Objetivo.** Los factores de riesgo (FR) asociados a la progresión de la infección en pacientes ya colonizados por bacterias gramnegativas resistentes a carbapenémicos (BGNRC) han sido abordados en pocos y dispersos trabajos. El objetivo de este estudio es identificar los factores de riesgo relevantes asociados a la progresión de la infección en pacientes con colonización del tracto respiratorio o rectal.

**Material y métodos.** Se realizó una revisión sistemática de la literatura para identificar los FR asociados a la progresión

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de la infección en pacientes con colonización del tracto respiratorio o rectal por BGNRC. Los FR identificados fueron luego evaluados y discutidos por el panel de expertos para identificar aquellos que son relevantes según la evidencia disponible y la experiencia de los expertos.

**Resultados.** Un total de 8 artículos fueron incluidos en el análisis de los FR en la colonización del tracto respiratorio y 21 para la colonización rectal, identificándose 19 FR asociados al desarrollo de neumonía y 44 FR asociados a la progresión de la infección respectivamente. Tras la sesión de discusión, los expertos acordaron que 13 FR se asociaban al desarrollo de neumonía tras la colonización del tracto respiratorio por BGNRC y 33 FR a la progresión de la infección tras la colonización rectal por BGNRC. La colonización del tracto respiratorio y rectal, la estancia previa en la UCI y una estancia prolongada en la UCI se clasificaron como FR relevantes independientemente del patógeno y del lugar de colonización. La exposición previa a antibióticos o el uso previo de carbapenémicos se clasificaron como FR relevantes para varios de los patógenos tanto en pacientes con colonización del tracto respiratorio como rectal.

**Conclusión.** Los resultados de este estudio pueden contribuir a la identificación precoz de los pacientes colonizados por BGNRC con mayor riesgo de desarrollo de infección, favoreciendo el uso temprano de terapias efectivas y mejorar los resultados en salud de estos pacientes.

**Palabras clave:** factor de riesgo, multirresistencia, bacterias gramnegativas resistentes a carbapenémicos; colonización; documento de consenso.

## INTRODUCTION

Multidrug-resistant (MDR) bacteria have become a relevant and urgent public health threat because few effective antibiotics are available for the treatment of infections caused by these bacteria. Among MDR pathogens, Gram-negative bacteria require special attention because of their resistance to carbapenems, the most active and potent agents available against MDR Gram-negative pathogens [1,2]. In 2017, the World Health Organisation published the list of priority pathogens for which innovative treatments are urgently needed. Carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacterales* are listed as the most critical pathogens [3]. In Spain, recently published studies show that carbapenem-resistant Gram-negative bacteria (CRGNB) are the cause of a high number of infections [4–6]. More specifically, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Enterobacterales* (including *Escherichia coli*, *Klebsiella pneumoniae* and *Enterobacter cloacae*) were the most common bacteria [4–6].

In most cases, these pathogens may colonize one or more patients' sites, constituting a silent and dangerous reservoir that can lead to the spread of these bacteria and a risk of development of associated clinical infections that may lead to clinical complications, including patient's death [7,8]. CRGNB colonisation prevalence has been studied on different

populations (e.g., patients undergoing organ transplants, general population, ICU patients) and is estimated to occur in 4% to 57% of the patients [9–12]. CRGNB may settle in different sites such as urinary tract, skin, or abdominal cavity. Among them, rectal and respiratory tract colonisation are of especial attention due to their high prevalence and the most common sites of screening with microbiological tests [13–15]. CRGNB, concretely *P. aeruginosa*, *A. baumannii* and *Enterobacterales*, have been identified as common rectal and respiratory tract colonizers [11,12].

In the last years, it has been suggested that colonisation is associated with clinical infection development and its potential consequences (e.g., septic shock) [7]. Risk factors (RFs) associated with CRGNB infection or colonisation have been widely studied [16–19]. Recently, an expert's consensus study performed in Spain has been published to help to clarify the RFs associated with CRGNB *P. aeruginosa* and *A. baumannii* infection development [20]. Factors associated with a risk for infection progression in already CRGNB colonised patients have been addressed in few and disperse works. Due to the lack of information and uncertainty regarding the RFs associated with infection progression from CRGNB rectal or respiratory tract colonisation, the main objective of this study is to provide clinical recommendations from an expert's consensus based on the current available evidence.

## MATERIAL AND METHODS

**Study design.** The study was designed in four different phases: **1)** Systematic literature review (SLR) to identify RFs associated to infection development after rectal or respiratory tract colonisation; **2)** Creation of the expert panel; **3)** Development of a questionnaire to evaluate identified RFs in SLR and **4)** Results analysis and consensus session.

### PHASE I: Systematic Literature Review

A SLR was conducted in October 2021 to identify the evidence available on RFs associated to clinical infection after respiratory tract (Site 1) and rectal (Site 2) CRGNB colonisation. The pathogens included for each site were *P. aeruginosa*, *A. baumannii*, and *Enterobacterales*, more specifically *Klebsiella pneumoniae* and *Escherichia coli*. The sources of information were biomedical databases such as MEDLINE, Cochrane Library and MEDES. The search strategy is depicted in Figure 1. Inclusion and exclusion criteria for each of the sites are described in Table 1 and Table 2. The population of study were adults for rectal colonisation, while for respiratory tract colonisation it was limited to adults in the ICU with mechanical ventilation. MeSH terms used for each site and pathogen are described in Supplementary Table 1.

### PHASE 2: Expert panel

A multidisciplinary panel consisting of 2 coordinators (an infectiologist and an intensivist) and 8 experts (2 intensivists, 3 infectiologists and 3 microbiologists) was created to review the RFs identified in the SLR and evaluate them for

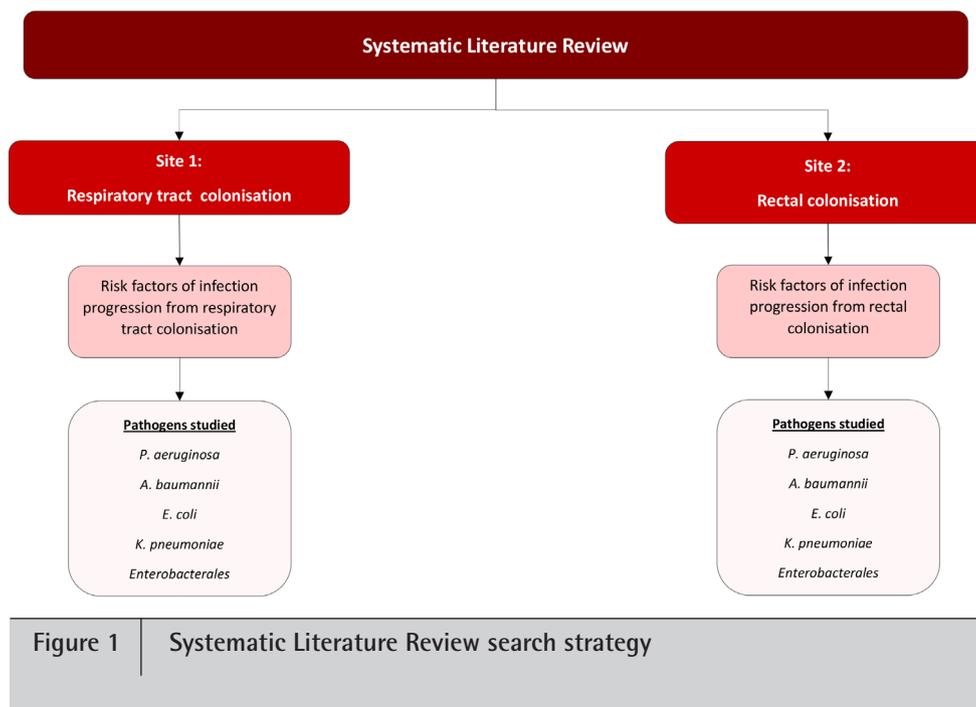


Figure 1 Systematic Literature Review search strategy

Table 1	Inclusion and exclusion criteria for respiratory tract colonisation SLR studies	
Site 1: Respiratory colonisation		
	Inclusion criteria	Exclusion criteria
	Articles including patients with respiratory colonisation caused by carbapenem-resistant Gram-negative bacteria, especially <i>P. aeruginosa</i> , <i>A. baumannii</i> , <i>Enterobacteriales</i> ( <i>E. coli</i> , <i>K. pneumoniae</i> ).	One-arm or pre-post studies.
	Works published in the last 5 years (2016-2021)	Studies from low- and middle-income countries.
	Publications in English or Spanish	Articles related with genetics
	Population: Adults (≥ 18 years), ICU inpatients with artificial airway	Articles including "COVID", "COVID-19", "coronavirus" or "SARS-CoV-2" infections
		Articles focused on base pathologies other than CRGNB infection (e.g., cystic fibrosis, bronchiectasis, chronic obstructive pulmonary disease)
		Paediatric population studies

Table 2	Inclusion and exclusion criteria for rectal colonisation SLR studies	
Site 2: Rectal colonisation		
	Inclusion criteria	Exclusion criteria
	Articles including patients with rectal colonisation caused by carbapenem-resistant Gram-negative bacteria focused on <i>P. aeruginosa</i> , <i>A. baumannii</i> , <i>Enterobacteriales</i> ( <i>E. coli</i> , <i>K. pneumoniae</i> ).	One-arm or pre-post studies
	Works published in the last 5 years (2016-2021)	Studies from low- and middle-income countries.
	Publications in English or Spanish	Articles related with genetics
	Population: Adults (≥18 years).	Articles including "COVID", "COVID-19", "coronavirus" or "SARS-CoV-2" infections
		Paediatric population studies

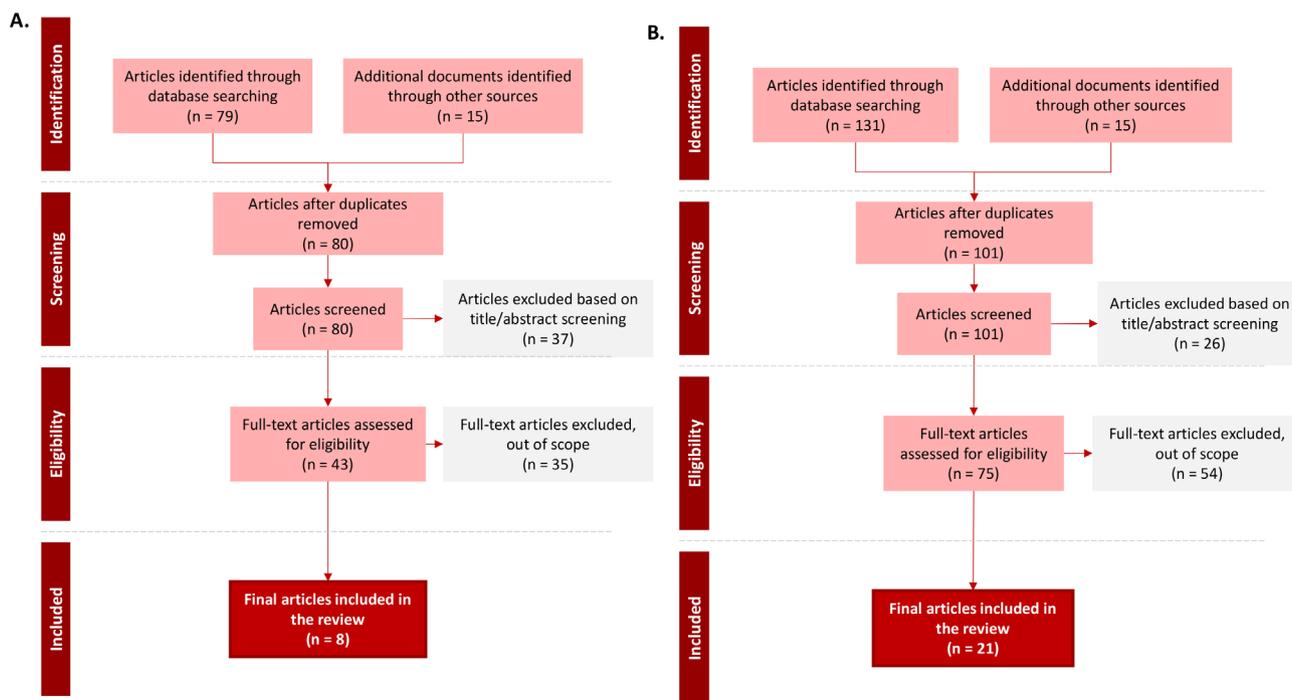


Figure 2 PRISMA diagram of literature review results for A. Respiratory tract CRGNB colonization and B. rectal CRGNB colonization.

its relevance based on available information and their own clinical experience. The Spanish experts were chosen based on their clinical experience in the study area, as well on their participation in similar studies published in indexed journals.

### PHASE 3: Development of materials to evaluate each of the RF identified in the SLR

For each article included in the SLR, a file was created to collect information in a systematic way. Information included for each article was: site of colonisation, pathogen, reference, year of publication, country, study design, setting, ward, inclusion criteria and exclusion criteria, total number of patients in the study and for each study group, type of statistical analysis and a summary of results of the univariate and multivariate analysis.

Together with the articles file, a questionnaire for each of the sites (respiratory tract and rectal colonisation) was developed to evaluate each of the RF by the expert panel. The questionnaire included all RF associated with infection development after CRGNB colonisation identified in the SLR. The questionnaire was then divided in two parts. **1) Evidence based**, which included RFs by pathogen associated with infection progression in colonised patients found in the SLR and presented for each pathogen. For each pathogen, two differentiated sections were assessed; RF commonly associated to infection progression and pathogen-specific RF. **2) Expert's opinion**, which included RF commonly associated to infection progression after CRGNB colonisation but were not found

in the SLR for a specific pathogen. Each RF was presented as a statement to assess its relevance, and a 3-point scale was used to evaluate it "1- I agree with the statement"; "2- I moderately agree with the statement" and "3- I disagree with the statement". Experts were asked to provide their rationale to their answer.

### PHASE 4 Results analysis and consensus session

The questionnaire and article files were sent to the experts. Experts were asked to evaluate the relevance of each RF related to infection progression after CRGNB colonisation based on the evidence available and their own clinical experience. In case there was no evidence, or they had no clinical experience, experts were asked to provide their expert opinion.

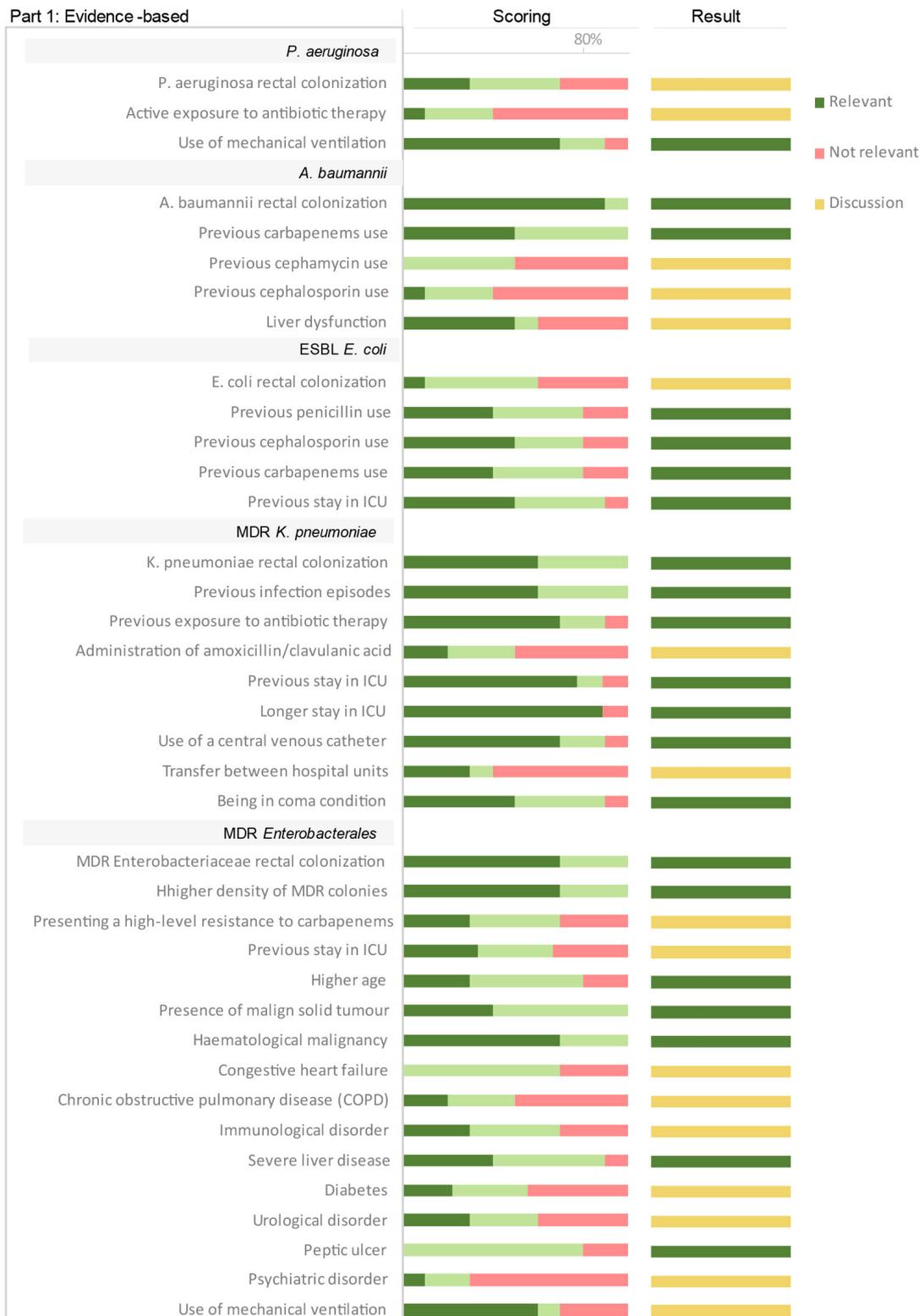
Results of the RF assessment were included in an excel database and were presented as a percentage of experts that answered each of the options. An arbitrary cut-off of 80% (8 out of 10) was set to determine agreement among the experts for each of the answers. The criteria agreed to include RF as relevant were: **1)** Acceptance of RFs with a score  $\geq 80\%$  with score "1- I agree" or "2 - I moderately agree". In case of a score  $\geq 80\%$  on the item "3- I disagree", the RF was excluded from the study. **2)** For those RF with  $< 80\%$  on any of the 3 scale items, those with  $\geq 80\%$  agreement when pooling "1- I agree" and "2- I moderately agree" were included as relevant. **3)** Those RF with  $< 80\%$  agreement after pooling "1- I agree" and "2- I moderately agree" were discussed during the consensus session. **4)** If



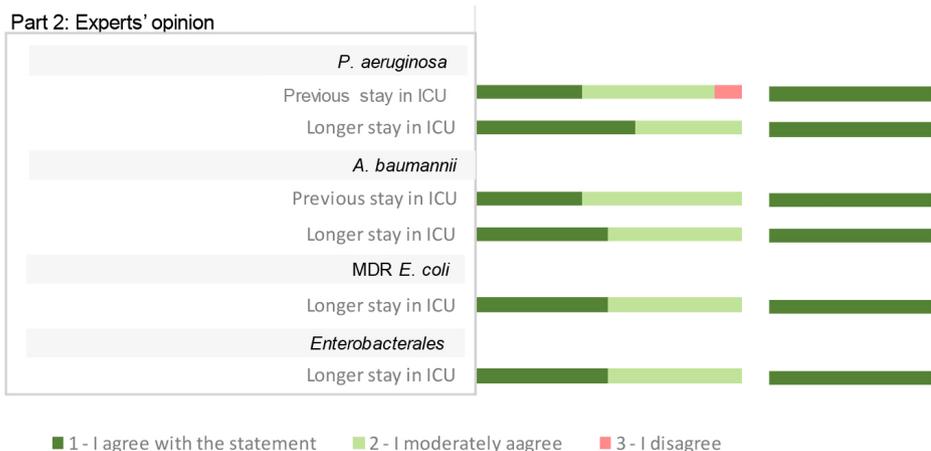
**Figure 3** Scoring and results of the assessment of risk factors associated with pneumonia progression after CRGNB respiratory tract colonization in ICU adult inpatients with mechanical ventilation. Scores are represented according to the percentage of responses on the 1- I agree, 2- moderately agree and 3- do not agree. Result column shows if the risk factor was included as relevant, not relevant, or needed to be discussed in the consensus session.

additional information or clarification was provided during the discussion session that changed the interpretation of the RF, the scoring could be reassessed and classified according to the above criteria. 5) The experts were able to exclude from the study those RFs that they considered ambiguous and difficult to interpret.

An online consensus session was performed in January 2022 to present the results and discuss the RF that did not reach consensus. For each RF to be discussed, a bar chart with the percentage of responses and a summary of statistical analysis of the studies where those RF were identified were presented. Finally, the RFs were accepted or excluded based on the previously described criteria.



**Figure 4A** Scoring and results of the assessment of risk factors identified in the literature associated with infection progression after CRGNB rectal colonization in adult population. Scores are represented according to the percentage of responses on the 1- I agree, 2- moderately agree and 3- do not agree. Result column shows if the risk factor was included as relevant, excluded, or discussed in the consensus session.



**Figure 4B** Scoring and results of the assessment of risk factors associated with infection progression after CRGNB rectal colonization in adult population according to expert's opinion. Scores are represented according to the percentage of responses on the 1- I agree, 2-moderately agree and 3- do not agree. Result column shows if the risk factor was included as relevant, excluded, or discussed in the consensus session.

## RESULTS

**Systematic Literature Review (SLR).** A total of 80 articles were identified in the SLR for the respiratory tract CRGNB colonisation site, and 8 articles were finally included. For rectal CRGNB colonisation site, a total of 101 were identified and 21 included in the review. PRISM diagrams of SLR results are included in Figure 2.

**Results analysis.** A total of 19 RF associated with pneumonia progression after respiratory tract CRGNB colonisation were identified and evaluated for its relevance by the expert panel. Out of 19 RF identified, 13 of them were included as relevant RF according to the agreed criteria, and 6 of them were discussed in the consensus session (Figure 3). Out of the 13 included as relevant, "respiratory tract colonisation" by *P. aeruginosa*, and "use of mechanical ventilation" in patients colonised by *A. baumannii* reached  $\geq 80\%$  in the score "1- I agree with the statement".

Regarding the rectal colonisation site, a total of 44 RF were identified to be associated with infection progression and evaluated for its relevance by the expert panel. Out of 44 RF identified, 27 of them were included as relevant RF according to the agreed criteria and 17 of them were discussed in the consensus session (Figure 4A and B). Out of the 27 included as relevant, "rectal colonisation" by *A. baumannii* and "longer stay in ICU" in patients colonised by *K. pneumoniae* reached  $\geq 80\%$  in the score "1- I agree with the statement". "Peptic ulcer" in patients with *Enterobacterales* colonisation also reach  $\geq 80\%$  in the score "2- I moderately agree with the statement".

**Consensus session.** The results from the questionnaire were presented to the expert panel for each of the sites (respiratory tract and rectal colonisation). According to the

established criteria, RFs that did not reach consensus in the previous exercise were presented for discussion.

Results after discussion and re-evaluation of RF associated with pneumonia development after respiratory tract colonisation in adult ICU inpatients with mechanical ventilation are described in Figure 5.

**In the respiratory tract RF discussion,** the panel agreed to include "ESBL-*Enterobacterales* respiratory colonisation" as a relevant RF for pneumonia development. On the other hand, experts reached consensus on excluding as relevant the following RFs for pneumonia development: "intake of vasopressors" and the "presence of solid cancer" in patients colonised with *P. aeruginosa*; "Diabetes" in patients colonised with *A. baumannii*; "administration of amoxicillin/clavulanic acid" in patients colonised with carbapenemase-producing *K pneumoniae*; "previous exposure to antibiotic therapy" in patients colonised with *Enterobacterales*.

The "intake of vasopressors" or "presence of solid cancer" were discarded by the experts due to study design of the evidence provided, which proved association but not causality [21,22]. In addition, the presence of solid cancer is a broad concept that should be nuanced (e.g. site, stage, immunocompromised status of the patient), as well the confusion factors associated, such as the treatment the patient receives [22]. Similar rationale was concluded when discussing "diabetes" as a RF. The study analysed the risk of infection recurrence and not infection progression, besides the fact that uncontrolled diabetes or patients' general condition would be more relevant factors than the presence of diabetes itself [23]. The RF "administration of amoxicillin/clavulanic acid" was excluded because even though there is a strong association according to the literature, it is not associated to an increased risk [24]. "Previous exposure to antibiotic therapy" in patients

	<i>P. aeruginosa</i>	<i>A. baumannii</i>	<i>K. pneumoniae</i>	<i>Enterobacterales</i>
Respiratory tract colonisation	Relevant	Relevant	Relevant	Relevant
Previous exposure to antibiotic therapy	Relevant	Relevant	Relevant	Not relevant
Intake of vasopressors	Not relevant	Not relevant	Not relevant	Not relevant
The presence of a solid cancer	Not relevant	Not relevant	Not relevant	Not relevant
Higher age	Not relevant	Relevant	Not relevant	Not relevant
Diabetes	Not relevant	Not relevant	Not relevant	Not relevant
Administration of amoxicillin/clavulanic acid	Not relevant	Not relevant	Not relevant	Not relevant
Previous infection episodes	Not relevant	Not relevant	Relevant	Not relevant
Use of mechanical ventilation	Not relevant	Relevant	Not relevant	Not relevant
Mechanical ventilation at ICU admission	Relevant	Not relevant	Not relevant	Not relevant
Previous stay in ICU	Relevant	Relevant	Relevant	Relevant
Longer stay in ICU	Relevant	Relevant	Relevant	Relevant

■ Relevant  
■ Not relevant

**Figure 5** Results after consensus of risk factors classified according to its relevance by pathogen in pneumonia progression after CRGNB respiratory tract colonisation in ICU adult inpatients with mechanical ventilation.

colonised with *Enterobacterales* was excluded being this RF associated to pathogen resistance development rather than pneumonia development.

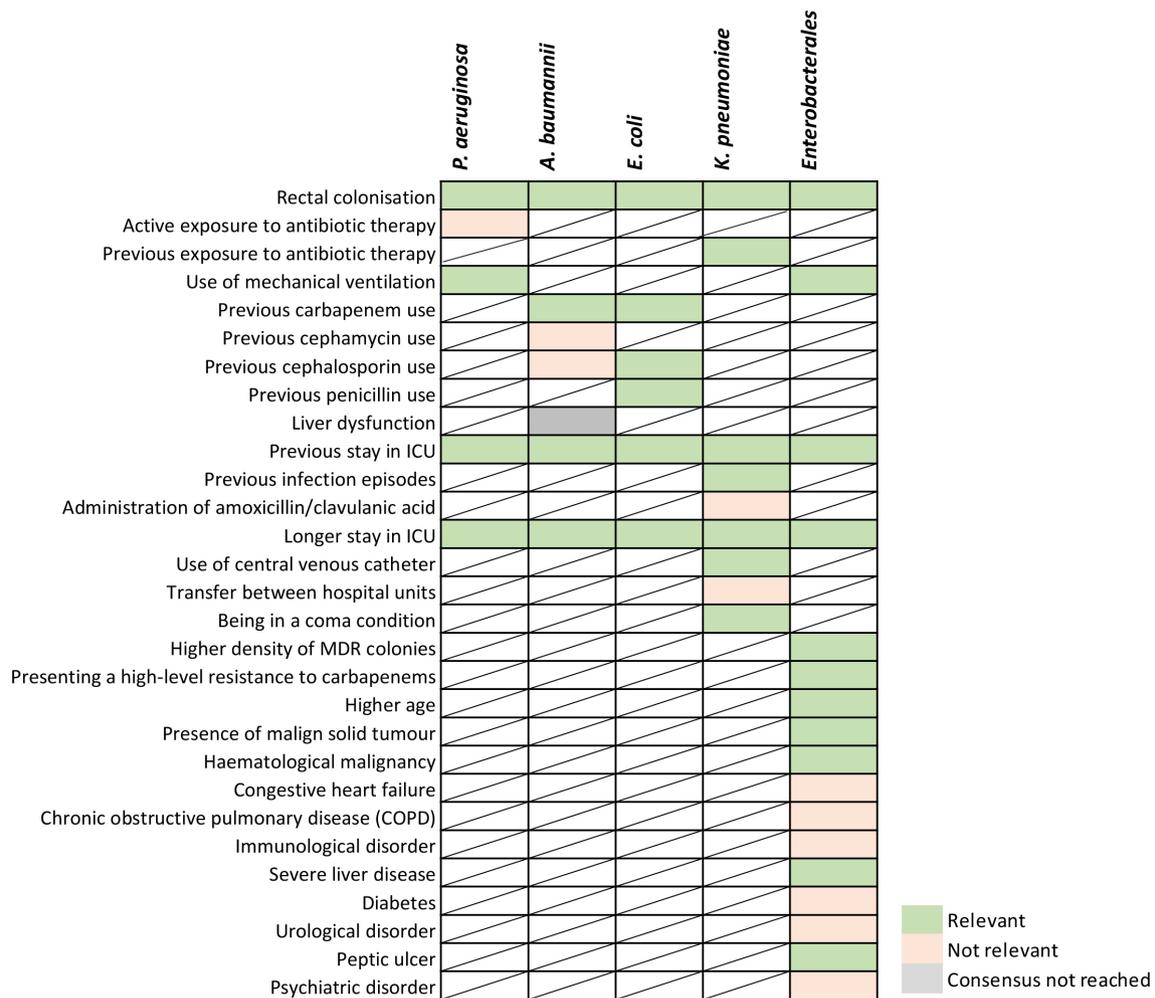
Results after discussion and re-evaluation of RF associated with infection after rectal colonisation in adult patients are described in Figure 6.

**During the rectal RF discussion**, out of 17 RF included in the discussion, the expert panel agreed to include 5 of the 17 discussed RF as relevant for infection development in rectal colonised patients: "*P. aeruginosa* rectal colonisation"; "ESBL *E. coli* rectal colonisation"; "Presenting a high-level resistance to carbapenems", "previous stay in ICU" and "use of mechanical ventilation" in patients with MDR *Enterobacterales* rectal colonisation. Consensus was not reached for the RF "Liver dysfunction" in patients colonised with *A. baumannii*, as approximately half of the experts considered it relevant due to the significant association proved in literature, while the other half considered that the disease description was too broad, lacking important information about the disease such as the grade or patient status.

On the other hand, the expert panel agreed on considering not relevant for infection development the following RFs: "Active exposure to antibiotic therapy" in *P. aeruginosa* rectal colonised patients; "previous cephamycin use" and "previous cephalosporin

use" in *A. baumannii* colonised patients; "administration of amoxicillin/clavulanic acid" and "Transfer between hospital units" in patients with MDR *K. pneumoniae* rectal colonisation; "Congestive heart failure", "Chronic obstructive pulmonary disease (COPD)", "Immunological disorder", "Diabetes", "urological disorder" and "psychiatric disorder" in patients with MDR *Enterobacterales* rectal colonisation.

The rationale behind excluding "Active exposure to antibiotic therapy" in patients colonised by *P. aeruginosa* was the same as in the respiratory tract site, being this RF associated to pathogen resistance development rather than pneumonia development [25]. "Previous cephamycin use", "previous cephalosporin use" and "administration of amoxicillin/clavulanic acid" were excluded because even though there is a strong association according to the literature, it is not associated to an increased risk [24,26]. "Transfer between hospital units" was excluded as that would depend on the units implicated (e.g., chronic vs. acute) [27]. "Congestive heart failure", "Chronic obstructive pulmonary disease (COPD)", "Immunological disorder", "Diabetes", "Urological disorder" and "Psychiatric disorder" were excluded as relevant RFs by the expert panel due to lack of significant association [10,28]. Furthermore, associated factors to these comorbidities such as disease stage, treatment received, or patient status could be relevant factors to be considered.



**Figure 6** Results after consensus of risk factors classified according to its relevance by pathogen in infection progression after CRGNB rectal colonisation in adult patients.

The evidence supporting each of the RFs identified in the SLR after consensus session are described in the Supplementary Table 2 and Supplementary Table 3.

### DISCUSSION

CRGNB colonisation constitute a silent and dangerous reservoir that can lead to the spread of these bacteria, in addition to the associated risk of developing clinical infections [7,8]. Identification of RFs associated with infection development in CRGNB colonised patients is important to assist physicians in identifying those patients at high risk that would require close monitoring or/and administration of early treatment. Nevertheless, few studies have been published analysing RFs associated with infection progression in CRGNB colonised patients.

In this study, a total of 181 articles were identified in the

SLR, 80 for the respiratory tract site and 101 for rectal site. Of these, 8 articles were finally included in the CRGNB respiratory tract colonisation and 21 for CRGNB rectal colonisation, identifying 19 RFs associated with pneumonia development and 44 RFs associated with infection progression, respectively. Most of RFs identified were supported by literature (74% of RF from the respiratory tract site and 86% of RF from rectal tract), and few were considered based on expert's experience and opinion (Supplementary Table 2 and Supplementary Table 3).

After discussion, the experts agreed on 13 RFs to be associated with pneumonia development after respiratory tract CRGNB colonisation and 33 RFs to be associated with infection progression after rectal CRGNB colonisation (Table 3). Consensus was not reached for the RF "Liver dysfunction" in patients colonised with *A. baumannii* in the rectal tract.

Noteworthy, respiratory tract and rectal colonisation,

<b>Table 3</b>		
<b>Risk factors associated to infection development in adult patients with CRGNB colonisation by site and pathogen.</b>		
	Risk factor associated with pneumonia development in patients with CRGNB respiratory tract colonisation admitted in the ICU and receiving artificial airway	Risk factor associated with the development of infections in patients with CRGNB rectal colonisation
<i>P. aeruginosa</i>	<i>P. aeruginosa</i> respiratory tract colonisation [22] Previous exposure to antibiotic therapy [21,22] Mechanical ventilation at ICU admission [29] Previous stay in ICU Long stay in the ICU	<i>P. aeruginosa</i> rectal tract colonisation [30] Use of mechanical ventilation [29] Previous stay in ICU Long stay in the ICU
<i>A. baumannii</i>	<i>A. baumannii</i> respiratory tract colonisation Previous exposure to antibiotic therapy [31] Higher age [31] Use of mechanical ventilation [31] Previous stay in ICU Long stay in the ICU [31]	<i>A. baumannii</i> rectal tract colonisation [26] Previous carbapenem use [26] Previous stay in ICU Long stay in the ICU
<i>E. coli</i>	N/A	<i>E. coli</i> rectal tract colonisation Previous carbapenem use [32] Previous cephalosporin use [32] Previous penicillin use [32] Previous stay in ICU [32] Long stay in the ICU
<i>K. pneumoniae</i>	<i>K. pneumoniae</i> respiratory tract colonisation Previous exposure to antibiotic therapy [24] Previous infection episodes [24] Previous stay in ICU Long stay in the ICU	<i>K. pneumoniae</i> rectal tract colonisation [10] Previous exposure to antibiotic therapy [24] Previous stay in ICU [33,34] Previous infection episodes [24,34] Longer stay in ICU [27] Use of central venous catheter [27,33] Being in a coma condition [33]
<i>Enterobacteriales</i>	<i>Enterobacteriales</i> respiratory tract colonisation [35] Previous stay in ICU Long stay in the ICU	<i>Enterobacteriales</i> rectal tract colonisation [28,35-37] Use of Mechanical ventilation [38] Previous stay in ICU [39] Long stay in the ICU Higher density of MDR colonies [35] Presenting a high-level resistance to carbapenems [36] Higher age [10] Presence of malign solid tumour [10,28] Haematological malignancy [10] Severe liver disease [28] Peptic ulcer [28]

previous stay in the ICU and longer stay in the ICU were classified as relevant RFs independently of the pathogen and site of colonisation. Previous exposure to antibiotic therapy or previous carbapenem use was also a common relevant RF for patients with CRGNB respiratory tract and rectal colonisation, supported by the literature and experts' opinion, showing altogether their relevance when identifying patients at high risk of infection development after CRGNB colonisation in those sites.

Other RFs identified are also consistent across

the sites, for instance "use of mechanical ventilation", "previous infection episodes", "higher age", or "pre-existing comorbidities", nevertheless the association is pathogen specific for each of the sites. The experts agreed that pre-existing comorbidities could be a relevant RF to identify patients at high-risk of infection development, nevertheless, those should be refined based on disease severity and patient status. Interestingly, some of the relevant RF associated to infection progression in this study have been associated with CRGNB infections in hospitalized patients in several studies, such as prior use of antibiotics, prior hospital or ICU stay and

length of stay [16–18].

The RFs that were excluded by the expert panel were generally due to the lack of significant association with increased risk in the literature, or because the study design was inadequate to answer the study question. In some cases, RF were excluded due to the existence of confounding factors that might be more relevant than the identified RFs themselves.

The limitations of this study are first, the low number of studies identified, due to the scarce evidence available, with most of the RFs identified being supported by only one study. Secondly, the design of the studies identified in the SLR, with different inclusion and exclusion criteria among them. Further prospective studies with less variability between patient populations would be needed, which would also make meta-analysis studies possible. For those reasons, the involvement of an expert panel with extensive experience in the field strengthens the study results.

To our knowledge, this study provides the best evidence available based on SLR and experts' opinion of the RFs associated with infection development in CRGNB colonised patients. The results of the study may contribute to the early identification of colonized patients at higher risk of infection development, favouring time-to-effective therapy and improving health outcomes.

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## CONFLICTS OF INTEREST

**RF** has participated as a speaker or consultant for MSD, Pfizer, Shionogi, Gilead, Grifols and Menarini. **AS** has participated in advisory meetings or as a speaker in educational activities for Pfizer, MSD, Angelini, Gilead Sciences and Shionogi. **RC** has participated in education activities organised by MSD, Pfizer and Shionogi and worked on research projects funded by MSD, Shionogi and Venatrox. **JLP** has participated in education activities and advisory meetings organised by Novartis, MSD, Pfizer and Gilead, Angelini and Shionogi and worked on research projects funded by Novartis. **CG-V** has received honoraria for talks on behalf of Gilead Science, MSD, Novartis, Pfizer, Janssen, Lilly, Shionogi as well as a grant from Gilead Science, Pfizer and MSD. **JG-M** has participated as a speaker in educational activities for MSD, Pfizer and Shionogi. **NL** has participated in advisory meetings or as a speaker in educational activities funded by Pfizer, MSD, Menarini and Shionogi. **PR** has participated as consultant and speaker in

educational activities organized by Pizer, MSD, Menarini and Shionogi. **MS** has collaborated in training or research projects and taken part in symposia, meetings or consultancies organised or funded by Gilead, MSD, Janssen, Pfizer and Shionogi. **VP** has participated in accredited educational activities sponsored by MSD, Pfizer and Shionogi and has been a consultant for Pfizer, Shionogi and Correvio. **AG-P** and **XB** are employees of Omakase Consulting S.L. that received funding from Shionogi Inc. to develop and conduct this study.

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