Review

Is It Possible to Eradicate Carbapenem-Resistant Acinetobacter baumannii (CRAB) from Endemic Hospitals?

Filippo Medioli 1, Erica Bacca 1, Matteo Faltoni 1, Giulia Jole Burastero 1, Sara Volpi 1, Marianna Menozzi 1, Gabriella Orlando 1, Andrea Bedini 1, Erica Franceschini 1, Cristina Mussini 2 and Marianna Meschiari 1,*

1 Department of Infectious Diseases, Azienda Ospedaliero-University of Modena, 41124 Modena, Italy; filippomediali@gmail.com (F.M.); erica.bacca@gmail.com (E.B.); matteo.faltoni@gmail.com (M.F.); g.burastero@gmail.com (G.J.B.); saravolpi@outlook.com (S.V.); marymenozzi@gmail.com (M.M.); gabriella.orlando07@virgilio.it (G.O.); andreakorlini@yahoo.com (A.B.); ericafranceschini0901@gmail.com (E.F.)

2 Clinic of Infectious Diseases, Department of Infectious Diseases, University of Modena, 41124 Modena, Italy; crimuss@unimore.it

* Correspondence: mariannameschiari1209@gmail.com; Tel.: +39-059-422-5830; Fax: +39-059-422-2604

Abstract: Background: Despite the global efforts to antagonize carbapenem-resistant Acinetobacter baumannii (CRAB) spreading, it remains an emerging threat with a related mortality exceeding 40% among critically ill patients. The purpose of this review is to provide evidence concerning the best infection prevention and control (IPC) strategies to fight CRAB spreading in endemic hospitals. Methods: The study was a critical review of the literature aiming to evaluate all available studies reporting IPC measures to control CRAB in ICU and outside ICU in both epidemic and endemic settings in the past 10 years. Results: Among the 12 included studies, the majority consisted of research reports of outbreaks mostly occurred in ICUs. The reported mortality reached 50%. Wide variability was observed related to the frequency of application of recommended CRAB IPC measures among the studies: environmental disinfection (100%); contact precautions (83%); cohorting staff and patients (75%); genotyping (66%); daily chlorhexidine baths (58%); active rectal screening (50%); closing or stopping admissions to the ward (33%). Conclusions: Despite effective control of CRAB spreading during the outbreaks, the IPC measures reported were heterogeneous and highly dependent on the different setting as well as on the structural characteristics of the wards. Reinforced ‘search and destroy’ strategies both on the environment and on the patient, proved to be the most effective measures for permanently eliminating CRAB spreading.

Keywords: gram-negative; Acinetobacter baumannii; carbapenemase; multi-drug resistance; carbapenem-resistant; outbreak; infection prevention; infection control; Acinetobacter baumannii carbapenemase; intensive care units

1. Introduction

Carbapenem-resistant Acinetobacter baumannii (CRAB) represents a major concern among carbapenem-resistant organisms (CRO) and is an emerging worldwide emergency. This pathogen finds its primary and exclusive spreading site into the healthcare setting [1,2].

According to the European Center for Disease Control (ECDC), CRAB has been identified as one of the 10 most frequently isolated microorganisms in ICU-acquired healthcare-associated infections (HAIs), accounting for 14.7% of pneumonia episodes, 8.1% of bloodstream infection (BSI), and for 7.1% of urinary tract infection (UTI) episodes in Italy [3]. The reported percentage of AMRI (Antimicrobial Resistance Index) associated with CRAB-ICU-acquired HAIs is 63.9% in Europe.

Such prevalence among HAI relates to the ability of A. baumannii to adhere to medical devices, including venous catheters (CVCs), urine catheters (CVs), and mechanical ventilation equipment, and its survival up to 33 days on dry surfaces [4,5]. Adhesion to various biotic and abiotic surfaces is the starting point for host colonization and infection.
Biofilm bacteria are 10–1000 times more resistant to antibiotic treatment than the planktonic phenotype [4].

Several studies have been trying to investigate risk factors for colonization and infection with A. baumannii [6–9]. Unfortunately, most of these studies are heterogeneous and conducted in different epidemiological settings, with many different selection criteria between cases and controls, thus not allowing to extract conclusive results.

Latibeaudiere et al. showed, though, that previous CRAB colonization increased the risk to develop a CRAB infection eight-fold [7].

Recently a retrospective matched case–control [6] with a prospective inclusion of cases and concurrent selection of controls, demonstrated via multivariable analysis that significant risk factors associated with CRAB colonization were use of permanent devices, mechanical ventilation, McCabe score, and carbapenem use. Different risk factors have been related to different clinical contexts (geriatric department: UCs and CVCs, fatal comorbidity, longer length of hospital stay; internal medicine department: partial disabilities or bedridden status, prolonged hospitalization, previous admission to the ICU + MV, permanent devices and catheters, current antibiotic therapy or antibiotic polytherapy; ICU: high McCabe Score, use of t3GC and carbapenems) [10].

Moreover, upon exposure to antibiotic-based disinfectants, bacteria respond by forming a subpopulation that persists and can become highly tolerant to antibiotics. This ‘selected’ subpopulation plays an essential role in the lingering of biofilm infections.

Moreover, the acquiring of carbapenem resistance leads to limited therapeutic options and this is linked with a high rate of mortality. Several strains developed the capacity to transmit resistance via mobile genetic elements that enable the production of carbapenemase enzymes [11]. This enhances the burst of outbreaks in healthcare settings. Thus, implementing a correct infection prevention and control (IPC) policy, involving all the healthcare professionals altogether, is essential.

CRAB outbreaks have mainly been reported in ICUs, during mechanical ventilation, after antibiotic treatment, and showed a higher mortality rate than Pseudomonas aeruginosa (47% vs. 23%) [7].

An important role has been played by the pandemic, since the latest European Antimicrobial Resistance Surveillance Network (EARS-Net) investigating the impact of the COVID-19 pandemic on antimicrobial resistance (AMR) underlines a decreasing trend of co-infection due to community pathogens in COVID-19 in-patients, in contrast with an excess of MDROs responsible for COVID-19 superinfections [12–15].

In particular, CRAB and vancomycin-resistant E. faecium were isolated more frequently in 2020 than in the previous years.

This event may be related to the fact that infection prevention and control (IPC) and antimicrobial stewardship (AS) programs have been compromised during the pandemic, leading to hospital-onset MDRO outbreaks [16–20].

In this emergent scenario, it is essential to better define which IPC interventions is relevant to eliminate CRAB from hospitals and should be considered an absolute priority. In general, a multimodal IPC approach, better if implemented as a ‘bundle’ of interventions, has been proven to be more effective [21–23].

In 2017, both ECDC and WHO guidelines were published in order to address this important issue.

The ECDC and WHO rigorously performed a systematic literature review to identify the best available evidence on the effective IPC measures to be applied for all at-risk patients upon admission to healthcare settings to prevent the transmission of all carbapenem-resistant organisms (CROs), including CRAB. The WHO document offers important additional suggestions for best practices to turn recommendations into adaptive work.

However, in both these guidelines, the quality of evidence on CRAB control were lowered from low to very low due to the scarce number and poor quality of the studies included. The described measures varied significantly in scope and evidence based [8,22].

Moreover, studies published after 2016 were obviously not included.
The consequences of this uncertainty are that it is still unclear which could be the best approach, especially when resources are limited, or times are challenging (like those of the COVID-19 pandemic).

The aim of this critical literature review is to identify the most effective IPC strategy to face the rising problem of CRAB spreading in hospitals worldwide.

2. Materials and Methods

We performed a critical literature review to assess published evidence on the control and prevention of CRAB in ICU during the last 10 years. As a first step, we decided to focus our review method on the infection control (IC) measures used for evidence grading in the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the infection control measures to reduce transmission of multidrug-resistant Gram-negative Bacilli (GNB), published in 2014 [21].

Hence, publications from 2012 to 2022 were outlined via an online literature search using PubMed.

We used the search criteria described below: *Acinetobacter AND CRAB OR Acinetobacter baumannii OR carbapenem-resistant Acinetobacter baumannii* AND (cross infection OR infection control OR infection prevention OR patient isolation OR cohorting OR gloves OR protective clothing OR handwashing OR hand hygiene OR sanitizer OR cleanser OR disinfectant OR preemptive isolation OR antisepsis OR disinfection OR sterilization OR environmental cleaning OR screening culture OR disease outbreaks OR management. Filters: from 2012–2022.

The articles extracted were then audited for meeting inclusion or exclusion criteria.

Inclusion Criteria:
A. The paper was published, but only full articles;
B. The paper was an epidemiological and/or outbreak report (both in endemic and in epidemic setting);
C. The responsible agent of the outbreak was CRAB;
D. The paper included description and assessment of IC measures deployed during the outbreak;
E. The paper included incidence and/or prevalence of the CRAB infection/colonization;
F. The outcome of the outbreak was described.

Exclusion Criteria:
A. In vitro data;
B. All other carbapenemases;
C. Only diagnostic data;
D. Case reports;
E. Reviews;
F. Other species than human.

The gathered IC measures were graded into major topics, based on the recommended measures to reduce transmission of CRAB from international agencies or international professional societies, i.e., the World Health Organization, the European Centre for Disease Prevention and Control, the U.S. Centers for Disease Control and Prevention, the U.S. Agency for Healthcare Research and Quality, and the European Society of Clinical Microbiology and Infectious Diseases [8,21,22,24,25].

The recorded measures consisted of hand hygiene; alcohol hand rub consumption; active rectal screening; additional active screening strategies; contact precautions and room isolation; alert code; daily chlorhexidine baths; staff/patient cohorting; closure/stop admissions; environmental disinfection; environmental cultures; monitoring of environmental cleaning; genotyping; and antimicrobial stewardship/monitoring of antibiotics consumption; training/education. The infection control studies were distinguished based on country origin, type of study, hospital setting, and department involved. The statistical method and final study outcomes were also assessed.
The outcome has been defined as a reduction in CRAB isolation during the reported period after the implementation of the mentioned IPC measures (as described in the ECDC guidelines, both for endemic and epidemic settings) [21].

3. Results

Our initial search query revealed 254 records, of which 58 met the inclusion criteria and were evaluated by full text. Finally, 12 articles were included that reported IPC measures for CRAB.

3.1. Study Characteristics

Table 1 summarizes the characteristics of the 12 included studies. The described studies and outbreaks reported data from all continents, supporting the potential for endemic spread of CRAB. Most of the studies described an epidemic outbreak (58%) while 42% occurred in endemic settings. The total duration of these studies was very heterogeneous, ranging from 3 months to 7 years.

| Study                          | Country | Type of Study     | Setting                      | Department Involved                        | ICU y/n | Statistical Method                        |
|--------------------------------|---------|------------------|------------------------------|-------------------------------------------|---------|------------------------------------------|
| Perez et al., 2020 [19]        | USA     | Outbreak Report  | Epidemic                     | Acute Care Hospital                       | No      | ITS: CRAB_ID decreased                   |
| Cho et al., 2014 [26]          | South Korea | Research support, Non-U.S. Gov'T | Endemic | Tertiary Hospital | No      | SR: CRAB_ID decreased                   |
| Munoz-Price et al., 2014 [27]  | USA     | Major Article    | Endemic                      | Major Hospital                            | Yes     | SR: CRAB hospital acquired cases decrease |
| Valencia-Martín et al., 2019 [28] | Spain | Research | Endemic                      | Intensive care Unit + adult wards         | Yes     | JP + ITS: SC decreased                   |
| Enfield et al., 2014 [29]      | USA     | Comparative Study | Epidemic                     | Intensive care Unit                       | Yes     | ITS: CRAB_ID decreased                   |
| Karampatakis et al., 2018 [30] | Greece | Epidemiological Study | Endemic                      | Intensive care Unit                       | Yes     | ITS: linear trend of CMA for CRAB infections increased |
| Eckardt et al., 2022 [31]      | USA     | Major Article    | Epidemic                     | Intensive care Unit                       | Yes     | ITS: CRAB_ID decreased                   |
| Chung et al., 2015 [32]        | South Korea | Research support, Non-U.S. Gov'T | Endemic                      | Intensive care Unit                       | Yes     | ITS: CRAB_ID decreased                   |
| Meschiari et al., 2020 [33]    | Italy   | Research         | Epidemic                     | Intensive care Unit                       | Yes     | ITSA: CRAB_ID decreased                  |
| Zhao et al., 2019 [34]         | China   | Research         | Epidemic                     | Intensive care Unit                       | Yes     | CS: prevalence of CRAB decreased         |
| Ben-chetrit et al. [35]        | Israel  | Research         | Epidemic                     | Intensive care Unit                       | Yes     | SR: CRAB_ID decreased                   |
| Metan et al., 2019 [36]        | Turkey  | Original Article | Epidemic                     | Neurological Intensive care Unit          | Yes     | BA: CRAB_ID decreased                   |

CRAB_ID CRAB, incidence density; CS, cross-sectional study; ICU, intensive care unit; ITS, interrupted time-series analysis; ITSA, intervention time series analysis; JP, jointpoint regression analysis; LC, linear change; SC, slope change; SR, segmented regression analysis; CMA, centered moving average; BA, before and after study.
The majority of the studies were performed in an ICU (83%). Four studies included data from outside an ICU setting [20,27–29]. None of the studies were set exclusively outside of an ICU. Regarding the ICU structure, only 5 out of 12 were ‘closed’ ICUs.

Concerning the statistical analysis conducted: half of the studies used an interrupted time-series analysis (ITS); three used a segmented regression analysis (SR); 1 a before and after study (BA); one used a cross-sectional study (CS); one used a joinpoint regression analysis (JP), even though this was combined with an ITS; and one was an intervention time series analysis (ITSA). Considering intervention outcomes: all except one study reported a significant reduction in CRAB post-intervention incidence. The duration of follow-up after the intervention ranged from 0 months (interrupting the observation at the end of the intervention) to 3 years after the intervention.

3.2. IPC Measures

Table 2 describes the most frequent components in infection prevention and control multimodal interventions implemented and their relative positive/negative impact on the outcome. All the studies adopted a multimodal approach with more than five different combined interventions.
Table 2. Most frequent components in infection prevention and control multimodal interventions implemented in the studies included.

| Study | HH Compliance/AHR Consumption | Active Rectal Screening (Targeted/Universal) | Additional Active Screening Strategies | Contact Isolation/Alert Code | Daily Chlorhexidine Baths | Cohorting Staff/patients | Closure/Stop Admissions | Environmental Disinfection | Environmental Cultures | Monitoring of Environmental Cleaning | Genotyping | Antimicrobial Stewardship/Monitoring of Antibiotic Consumption | Training/Education | Outcome |
|-------|-----------------------------|---------------------------------------------|---------------------------------------|----------------------------|--------------------------|---------------------------|---------------------------|---------------------------|--------------------------|-------------------------------------|------------|-------------------------------------------------|------------------|---------|
| Perez et al., 2020 [19] | | | | | | | | | | | | | | |
| Cho et al., 2014 [26] Munoz-Price et al., 2014 [27] Valencia-Martín et al., 2019 [28] | | | | | | | | | | | | | | |
| Enfield et al., 2014 [29] | | | | | | | | | | | | | | |
| Karampatakis et al., 2018 [30] | | | | | | | | | | | | | | |
| Eckardt et al., 2022 [31] | | | | | | | | | | | | | | |
| Chung et al., 2015 [32] | | | | | | | | | | | | | | |
| Meschiari et al., 2020 [33] | | | | | | | | | | | | | | |
### Table 2. Cont.

| Study                                      | HH Compliance/AHR Consumption | Active Rectal Screening (Targeted/Universal) | Additional Active Screening Strategies | Contact Isolation /Alert Code | Daily Chlorhexidine Baths | Cohorting Staff/patients | Closure/Stop Admissions | Environmental Disinfection | Environmental Cultures | Monitoring of Environmental Cleaning | Genotyping | Antimicrobial Stewardship/Monitoring of Antibiotic Consumption | Training/Education | Outcome |
|-------------------------------------------|-------------------------------|---------------------------------------------|--------------------------------------|-------------------------------|---------------------------|--------------------------|-------------------------|---------------------------|--------------------------------|--------------------------|----------------------------------|-------------------|----------|
| Zhao et al., 2019 [34]                    | Green                         | Red                                         | Yellow                               | Green                        | Red                       | Green                    | Red                     | Red                       | Green                    | Red                     | Yellow                           | Gray               | Green   |
| Ben-chetrit et al. [35]                   | Yellow                        | Yellow                                      | Green                                | Yellow                        | Yellow                    | Yellow                   | Yellow                  | Yellow                    | Yellow                  | Yellow                 | Yellow                           | Yellow             | Yellow  |
| Metan et al., 2019 [36]                   | Yellow                        | Yellow                                      | Green                                | Yellow                        | Yellow                    | Yellow                   | Yellow                  | Yellow                    | Yellow                  | Yellow                 | Yellow                           | Yellow             | Yellow  |
| All studies                               | Yellow                        | Yellow                                      | Green                                | Yellow                        | Yellow                    | Yellow                   | Yellow                  | Yellow                    | Yellow                  | Yellow                 | Yellow                           | Yellow             | Yellow  |

Legend: AHR, alcohol-based hand rubs; BA, before and after study; BHI, brain–heart infusion medium; CMA, centered moving average; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRAB_ID CRAB, incidence density; CS, cross-sectional study; DDD, defined daily doses; ERIC-PCR, Enterobacterial repetitive intergenic consensus; HH, hand hygiene; ICU, intensive care unit; NA, not available; PGFE, pulsed-field gel electrophoresis; BA, before and after analysis; WGS, whole-genome sequencing.
The implemented IPC measures were: environmental disinfection (100%) more frequently performed with 10% sodium hypochlorite; hand hygiene and/or alcohol-based hand rub consumption (91%); contact precautions (83%); staff education (83%); additional active screening (83%); cohorting staff and patients (75%); monitoring of environmental cleaning (66%); genotyping (66%); daily chlorhexidine baths (58%); antimicrobial stewardship/monitoring of antibiotic consumption (58%); active rectal screening (50%); environmental cultures (41%); and closing or stopping admissions to the ward (33%).

Contact precaution was considered an essential component for CRAB control and was universally applied by all studies, while the use of single rooms or rather than enhanced cohorting using a separate intensive care module varied across studies. One study adopted universal contact precaution until the patient was discharged independently of CRAB status. Overall, 9 out of 12 of the studies adopted a cohorting strategy (2 did not mention such strategy).

Staff or nursing cohorting was mentioned in three of the studies [29–31]. Enhanced training and staff education was achieved in all except two studies. However, many studies did not specify the implementation model.

Unexpectedly, the implementation of hand hygiene best practices was described in only eight of the studies, and alcohol hand rub consumption was described only in five of the studies.

Only three of the studies, in fact, thoroughly depicted the implementation methodology they used.

More specifically, Cho et al. reported the promotion of hand hygiene using alcohol-based hand gel (ABHG) without any further description or registration of the intervention [26]. Chung et al. stated that they followed the current guidelines according to hand hygiene [32], without subsequent implementation. Valencia-Martín et al. provided both training and structured observation on hand hygiene, without focusing on alcohol-based hand rub consumption [28].

Enfield et al. measured hand hygiene compliance through a covert, observation program that has been used at UVAMC since 2006 (no further description was provided) [29].

Munoz-price et al., on the other hand, described how, in their intervention, hand imprints were sporadically obtained from the staff. The plates with bacterial growth were then returned to the units and shown to health professionals to explain the potential role of their hands in the spreading of bacteria. Moreover, positive plates were published as examples in the weekly electronic communications. Finally, hand hygiene messages were placed via posters with pictures of hospital leadership personnel [27].

Active surveillance screening was widely varied depending on the surveillance site, the number of samples, and their frequency. Seven out of twelve adopted rectal screening, three out of thirteen (Metan, Meschiari, and Eckardt) added systematically the screening of axilla and groin; Perez also added the respiratory tract samples but with a random recurrence. Moreover, Valencia-Martín et al. were able to reach a sensitivity of 96% combining rectal and pharyngeal swabs, compared to the 78% obtained with rectal swab only. Combining the overall results of the studies, the best performance has been obtained with skin samples (100%), followed by rectal samples (86%) [29]. The frequency of repeated screenings was also variable: half of the studies, screened actively, starting from ICU admission then repeated once a week. For the others, screening ranged from twice per week to once every two weeks.

Whole-genome sequencing analysis (WGS) was applied only by 25% of studies.

4. Discussion

The literature, regarding CRAB, contains information that are extremely variable from many different settings worldwide. Therefore, even after a thorough selection of articles, it remains difficult to describe a pattern of interventions that could be universally effective. Nonetheless, we were able to identify the most used and the most effective measures
against CRAB in those that we deemed to be the most representative experiences of the last 10 years. Furthermore, by including very different studies in terms of setting (both endemic and epidemic) and country of origin, our study allows us to validate the effectiveness of interventions in geographical areas that differ widely in terms of incidence rates and availability of resources.

Indeed, the CRAB prevalence in the mentioned countries varies as follows: USA 30% (25–35%); South Korea 77% (71–82%); Greece 94% (92–95%); Spain 58% (47–68%); China 82% (80–84%); Turkey 91% (90–92%); and Italy 80% (78–82%) [37,38]. Therefore, the wide variability gave us the possibility to describe how to control CRAB spreading in those countries for which the most are epidemiologically affected by this pathogen [39].

Concerning the statistical method used to define the results, only half of the studies used an interrupted time-series analysis to evaluate their outcomes and only one study used an intervention time-series analysis that demonstrated that an ICP bundle including enhanced environmental cleaning had a decisive impact on nosocomial CRAB ICU incidence density against a background of stable AHR and antibiotic use [33].

Importantly, only these analyses could provide an appropriate evaluation of ICP measures because it provides an overview of the well-distributed effectiveness over time, enriching the assessment methodology with quality [11,40].

Furthermore, to provide evidence of the sustainability of the intervention performed, it is important to use a long post-intervention follow-up. Most of the studies included (9 out of 12) measured their interventions during a time lapse that ranged from 1 year to 7 years [26–30,32–35].

Another relevant consideration is that the CRAB burden seems to affect the intensive care setting more significantly; only a few studies have addressed this issue outside ICU. Further studies would be required to investigate the burden of this pathogen in non-intensive areas and to demonstrate whether the proposed interventions could be equally effective.

Importantly, the impact of ICP measures in ICUs could also be influenced by the open versus closed structure.

There is good evidence that closed ICUs are associated with better outcomes and better quality of care, other than being less prone to wide-spread infections by MDROs, indeed, closed ICUs allow easier implementation of contact precautions and cohorting of patients than open areas.

However, as our review shows, these formats are increasing lacking, and the implementation of ICP strategies must deal with these structural limitations. Strategies to control CRAB outbreaks often require positive patients’ relocation to a cohort ward and sometimes even lead to temporary closure of the ICU. Therefore, contact isolation, which was confirmed as a key strategy for CRAB control, implemented in all the studies reviewed, cannot always be performed by placing CRAB colonized/infected patients in a single room. Similarly, patient cohorting is extremely difficult to apply in open space units. On the other hand, it is equally impossible to close ICU if it is the only one in the hospital or during an epidemic period such as the recent COVID-19 pandemic.

In countries with limited resources and unfavorable structures, other than in pandemic periods, Meschiari et al. suggested, wherever the setting is an open space, innovative solutions such as cycling radical cleaning and disinfection. This procedure can be easily implemented in open-space ICUs and avoids ICU closure and limited admissions.

Contact isolation is strictly linked to active surveillance, applied in the 83% of the revised studies. Active screening for early detection and control of CRAB, while strongly recommended for carbapenem-resistant Enterobacteriaceae (CRE), is still strongly debated.

For instance, ECDC guidelines suggest applying active screening, as for CRE, by obtaining swabs from rectal or perirectal areas, and any other site that is either actively infected or considered to be colonized [32]; on the other hand, ESCMID guidelines underline that the detection of a CRAB carrier may be affected by the low sensitivity of the conventional methods. The WHO guidelines did not address this important topic [29].
Only Tacconelli et al., quoting the Association for Professionals in Infection Control and Epidemiology (APIC) guide for the control of MDR-\textit{A. baumannii}, suggested to culture multiple patient sites including the nose, throat, axilla, groin, rectum, open wounds and/or tracheal aspirates \cite{21,41}.

Accordingly, to these heterogenous recommendations, our review confirmed different approaches of active screening at country level.

Our findings suggested that, for endemic situations, it was sufficient to maintain active surveillance within 48 h of ICU admission with a rectal swab; during outbreaks, surveillance must be implemented weekly, granted by rectal swabs, and adding at least three other different body areas (axilla, groin, and trachea were specifically the most used).

It is important to note that since the results of the CRAB screening are not immediately available, and that the timing of application of the different measures depends on the method used (molecular PCR or phenotypical culture), our previous work suggested to apply preventive contact precautions to all the ICU patients until the end of the outbreak \cite{24}.

Unfortunately, the implementation of hand hygiene best practices was described in only eight of the studies, and alcohol hand rub consumption data were collected only in five of the studies.

Effective hand hygiene compliance is widely recognized and strongly recommended, both by the WHO and ECDC \cite{8,22}, to reduce healthcare-associated infection transmission; thus, it should be a standard of care and is not outlined among interventions \cite{11}. Moreover, it seems crucial, especially during outbreaks, to conduct specific audits and feedback on hand hygiene direct compliance, which is better if in the field, and only one study seemed to use this approach \cite{42}. Alcohol-based hand rub (ABHR) consumption is depicted as a valid alternative and/or addition to hand hygiene implementation in the guidelines, even though according to our review, only a few studies reported the percentage of ABHR use during the study period.

Unexpectedly, despite CRAB being well-known for being strongly environmentally resistant as well as a biofilm producer, environmental screening, and subsequent disinfection of colonized surfaces, it was described only in half of the studies reviewed. Its role is extremely debated, and only conditionally recommended \cite{22} (only WHO guidelines mention environmental screening), because the traditional method of environmental sampling suffers from low sensitivity and requires an important consumption of human resources, other than a massive cooperation with the microbiology laboratory.

To overcome the limitation due to poor sensitivity, Meschiari et al. used a brain–heart infusion (BHI) moistened sterile gauze technique because in their experience it proved to be far more sensitive than standard sampling methods (40% positives vs. 0%; \( p < 0.05 \)). More than 50% of the environmental samples in that study were positive for CRAB \cite{38}, while instead, the other studies that gathered environmental sampling did not describe the use of such a methodology.

On the other hand, 100% of the studies performed environmental cleaning, confirming its crucial role for CRAB eradication. In this regard, the disinfectant used did not seem to be essential (9 out of 12 (75%) of the studies used sodium hypochlorite), but rather the certainty of the cleaning and biofilm complete removal.

The evidence that seemed to support the use of new technologies, such as the peroxide or the UV rays, was recently disproved \cite{43-45}.

Concerning patient decolonization, the evidence for effectiveness of chlorhexidine gluconate (CHG) bathing against CRAB is a relatively recent finding. This could be the reason why only seven of the studies utilized daily chlorhexidine baths for the patients. The 2014 ESCMID guidelines did not recommend the universal use of chlorhexidine because of a lack of evidence concerning the reduction in bloodstream infections due to Gram-negative bacilli \cite{21}. Nevertheless, they mentioned some successful bundles that included chlorhexidine baths.
Concerning the importance of implementation of training and education and the composition of the infection control team, unfortunately only three of the studies went into detail about what professionals were included into the intervention (namely nurses, ICU physicians, infectious disease physicians, and microbiologists). Further studies about this matter may be required [27,28,33].

A recent study by Fan et al. [46] suggests that chlorhexidine bathing significantly reduces CRAB colonization in the ICU setting.

To provide useful information on the CRAB transmission dynamic, only some of the studies used advanced genotyping methods (66%), both for patient and environmental screening. Unfortunately, next-generation sequencing was applied only by 25% of the studies included. Specifically, our finding underlined that only WGS proved to be a valuable tool for identification of the sustained reservoirs.

The issue of therapy to control CRAB must be addressed as selective pressure and carbapenem sparing [47]. For this very reason, 7 out of 12 of the papers reviewed focused on antimicrobial stewardship, and especially focused on the carbapenem sparing part, reducing, in all cases, the prevalence of CRAB. It seems that of vital importance in involving infectious diseases, physicians, microbiologists, and pharmacologists into a stewardship program, to decrease the resistance pressure on colonizing *Acinetobacter baumannii*.

These results emphasize how it will be essential for the future to invest economical resources to reach more profitable results.

Our critical review certainly has limitations; it is not a systematic review, and we used only one database for the research (PubMed).

Moreover, due both to the limited number of studies published addressing this issue, and their extreme variability in terms of methodology, study design, setting, outcome, and duration of follow-up after intervention, it was impossible to obtain a direct comparison as well as the possibility of publication bias demonstrating the effectiveness of certain IPC measures in CRAB hospital eradication. This should be considered in view of the included studies.

5. Conclusions

The impact of every single IC measure against the spreading of CRAB remains difficult to assess. The quality of the evidence published so far is still low, and there is a lack of controlled intervention studies.

Even if variability in outcomes and measures, along the studies, is still wide, the implementation of multimodal measures achieved a significant reduction in CRAB infection and CRAB-related deaths. Reinforced ‘search and destroy’ strategies both on the environment and on the patient, proved to be the most effective measures for permanently eliminating CRAB spreading.

Our results underline how intervention bundles should be coherent with the setting where they are applied. The COVID-19 pandemic demonstrated that open-space ICUs promoted the transmission of pathogens with greater environmental resistance, such as CRAB. Therefore, it is of vital importance to develop strategies that allow to maintain open wards and do no limit access, either in ICUs or any other ward in order to overcome nosocomial outbreaks without limiting or even stopping healthcare activities.

**Author Contributions:** Conceptualization, M.M. (Marianna Meschiari); data curation, F.M.; investigation, M.M. (Marianna Meschiari), E.B., F.M., M.F. and S.V.; methodology, M.M. (Marianna Meschiari) and F.M.; supervision, M.M. (Marianna Meschiari) and C.M.; writing—original draft, F.M. and M.M. (Marianna Meschiari); writing—review and editing, G.J.B., E.F., A.B., G.O., M.M. (Marianna Menozzi), M.M. (Marianna Meschiari) and C.M. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Conflicts of Interest:** All authors have no conflict to declare.
References

1. World Health Organization. *Prioritization of Pathogens to Guide Discovery, Research, and Development of New Antibiotics for Drug Resistant Bacterial Infections, including Tuberculosis*; World Health Organization: Geneva, Switzerland, 2017. Available online: https://www.who.int/publications/i/item/WHO-EMP-IAU-2017.12 (accessed on 16 May 2022).

2. Perez, F.; Van Duin, D. Carbapenem-resistant Enterobacteriaceae: A menace to our most vulnerable patients. *Clevel. Clin. J. Med.* 2013, 80, 225–233. [CrossRef] [PubMed]

3. European Centre for Disease Prevention and Control. Healthcare-Associated Infections Acquired in Intensive Care Units. In ECDC: *Annual Epidemiological Report for 2017*; European Centre for Disease Prevention and Control (ECDC): Stockholm, Sweden, 2019.

4. Jawad, A.; Seifert, H.; Snelling, A.M.; Heritage, J.; Hawkey, P.M. Survival of *Acinetobacter baumannii* on Dry Surfaces: Comparison of Outbreak and Sporadic Isolates. *J. Clin. Microbiol.* 1998, 36, 1938–1941. [CrossRef] [PubMed]

5. Polotto, M.; Casella, T.; Tolentino, F.M.; Mataruco, M.M.; Porto, N.K.M.; Binhardi, M.F.B.; Nogueira, M.C.L. Investigation of carbapenemases and aminoglycoside modifying enzymes of *Acinetobacter baumannii* isolates recovered from patients admitted to intensive care units in a tertiary-care hospital in Brazil. *Rev. Soc. Bras. Med. Trop.* 2020, 53, e20190044. [CrossRef] [PubMed]

6. Meschiari, M.; Kaleci, S.; Orlando, G.; Selmi, S.; Santoro, A.; Bacca, E.; Menozzi, M.; Franceschini, E.; Puzzolante, C.; Bedini, A.; et al. Risk factors for nosocomial rectal colonization with carbapenem-resistant *Acinetobacter baumannii* in hospital: A matched case–control study. *Antimicrob. Resist. Infect. Control* 2021, 10, 69. [CrossRef]

7. Latibeaudiere, R.; Rosa, R.; Laowansiri, P.; Arheart, K.; Namias, N.; Munoz-Price, L.S. Surveillance Cultures Growing Carbapenem-Resistant *Acinetobacter baumannii* Predict the Development of Clinical Infections: A Retrospective Cohort Study. *Clin. Infect. Dis.* 2015, 60, 415–422. [CrossRef] [PubMed]

8. Magiorakos, A.P.; Burns, K.; Baño, J.R.; Borg, M.; Daikos, G.; Dumpis, U.; Lucet, J.C.; Moro, M.L.; Tacconelli, E.; Simonsen, G.S.; et al. Infection prevention and control measures and tools for the prevention of entry of carbapenem-resistant Enterobacteriaceae into healthcare settings: Guidance from the European Centre for Disease Prevention and Control. *Antimicrob. Resist. Infect. Control* 2017, 6, 113. [CrossRef] [PubMed]

9. European Centre for Disease Prevention and Control. ECDC Technical Report: *Risk Assessment on the Spread of Carbapenemase-Producing Enterobacteriaceae (CPE) through Patient Transfer between Healthcare Facilities, with Special Emphasis on Cross-Border Transfer*; European Centre for Disease Prevention and Control: Stockholm, Sweden, 2011.

10. Lortholary, O.; Fagon, J.-Y.; Hoi, A.B.; Slama, M.A.; Pierre, J.; Giral, P.; Rosenzweig, R.; Gutmann, L.; Safar, M.; Acar, J. Nosocomial Acquisition of Multiresistant *Acinetobacter baumannii*: Risk Factors and Prognosis. *Clin. Infect. Dis.* 1995, 20, 790–796. [CrossRef]

11. Tomczyk, S.; Zanichelli, V.; Grayson, M.L.; Twyman, A.; Abbass, M.; Pires, D.; Allegranzi, B.; Harbarth, S. Control of Carbapenem-resistant Enterobacteriaceae, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* in Healthcare Facilities: A Systematic Review and Reanalysis of Quasi-experimental Studies. *Clin. Infect. Dis.* 2019, 68, 873–884. [CrossRef] [PubMed]

12. Tamma, P.D.; Attken, S.L.; A Bonomo, R.; Mathers, A.J.; van Duin, D.; Clancy, C.J. Infectious Diseases Society of America Guidance on the Treatment of AmpC β-Lactamase–Producing Enterobacterales, Carbapenem-Resistant *Acinetobacter baumannii*, and Stenotrophomonas maltophilia Infections. *Clin. Infect. Dis.* 2021, 74, 2089–2114. [CrossRef] [PubMed]

13. Russo, A.; Gavaruzzi, F.; Ceccarelli, G.; Borrazzo, C.; Oliva, A.; Alessandri, F.; Magnanini, E.; Pugliese, F.; Venditti, M. Multidrug-resistant *Acinetobacter baumannii* infections in COVID-19 patients hospitalized in intensive care unit. *Infection* 2022, 50, 83–92. [CrossRef]

14. Thoma, R.; Seneghini, M.; Seifert, S.N.; Vuichard Gysin, D.; Scanferla, G.; Haller, S.; Flury, D.; Boggian, K.; Kleger, G.R.; Filipovic, M.; et al. The challenge of preventing and containing outbreaks of multidrug-resistant organisms and Candida auris during the coronavirus disease 2019 pandemic: Report of a carbapenem-resistant *Acinetobacter baumannii* outbreak and a systematic review of the literature. *Antimicrob. Resist. Infect. Control* 2022, 11, 12. [CrossRef]

15. Rangel, K.; Chagas, T.P.G.; De-Simone, S.G. *Acinetobacter baumannii* Infections in Times of COVID-19 Pandemic. *Pathogens* 2021, 10, 1006. [CrossRef] [PubMed]

16. Lötisch, F.; Albigier, B.; Monnet, D.L.; Struelens, M.J.; Seifert, H.; Kohlenberg, A.; European Antimicrobial Resistance Genes Surveillance Network (EURGen-Net): Carbapenem-Resistant *Acinetobacter baumannii* Capacity Survey Group. Epidemiological situation, laboratory capacity and preparedness for carbapenem-resistant *Acinetobacter baumannii* in Europe, 2019. *Eurosurveillance* 2020, 25, 2001735. [CrossRef]

17. Baker, M.A.; F Sands, K.; Huang, S.S.; Kleinman, K.; Septimus, E.J.; Varma, N.; Blanchard, J.; E Poland, R.; Coady, M.H.; Yokoe, D.S.; et al. The Impact of Coronavirus Disease 2019 (COVID-19) on Healthcare-Associated Infections. *Clin. Infect. Dis.* 2021, 74, 1748–1754. [CrossRef] [PubMed]

18. Weiner-Lastinger, L.; Pattabiraman, V.; Konnor, R.; Patel, P.; Wong, E.; Xu, S.Y.; Smith, B.; Edwards, J.R.; Dudeck, M. The impact of coronavirus disease 2019 (COVID-19) on healthcare-associated infections in 2020: A summary of data reported to the National Healthcare Safety Network. *Infect. Control Hosp. Epidemiol.* 2022, 43, 12–25. [CrossRef] [PubMed]

19. Perez, S.; Innes, G.K.; Walters, M.; Mehr, J.; Arias, J.; Greeley, R.; Chew, D. Increase in Hospital-Acquired Carbapenem-Resistant *Acinetobacter baumannii* Infection and Colonization in an Acute Care Hospital during a Surge in COVID-19 Admissions—New Jersey, February–July 2020. *MMWR. Morb. Mortal. Wkly. Rep.* 2020, 69, 1827–1831. [CrossRef]

20. Antimicrobial Consumption in the EU/EEA (ESAC-Net)—Annual Epidemiological Report for 2020. Available online: https://www.ecdc.europa.eu/en/antimicrobial-consumption/surveillance-and-disease-data/database (accessed on 18 November 2021).
21. Tacconelli, E.; Cataldo, M.A.; Dancer, S.J.; De Angelis, G.; Falcone, M.; Frank, U.; Kahlmeter, G.; Pan, A.; Petrosillo, N.; Rodriguez-Baño, J.; et al. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. *Clin. Microbiol. Infect.* 2014, 20 (Suppl. 1), 1–55. [CrossRef] [PubMed]

22. World Health Organization. *Guidelines for the Prevention and Control of Carbapenem-Resistant Enterobacteriaceae, Acinetobacter baumannii and Pseudomonas aeruginosa in Health Care Facilities*; World Health Organization: Geneva, Switzerland, 2017. Available online: https://apps.who.intiris/handle/10665/259462 (accessed on 27 May 2022).

23. Tacconelli, E.; Buhl, M.; Humphreys, H.; Malek, V.; Presterl, E.; Rodriguez-Baño, J.; Vos, M.C.; Zingg, W.; Mutters, N.T. Analysis of the challenges in implementing guidelines to prevent the spread of multidrug-resistant gram-negatives in Europe. *BMJ* Open 2019, 9, e027683. [CrossRef] [PubMed]

24. US Centers for Disease Control and Prevention (CDC). *Facility Guidance for Control of Carbapenem-Resistant Enterobacteriaceae (CRE)—November 2015 Update CRE Toolkit; Centers for Disease Control and Prevention: Atlanta, GA, USA, 2015.*

25. Agency for Healthcare Research and Quality. *Carbapenem-Resistant Enterobacteriaceae (CRE) Control and Prevention Toolkit; Content Last Reviewed April 2014; Agency for Healthcare Research and Quality: Rockville, MD, USA, 2014.* Available online: https://www.ahrq.gov/hai/patient-safety-resources/cre-toolkit/index.html (accessed on 1 May 2022).

26. Cho, O.H.; Bak, M.H.; Baek, E.H.; Park, K.-H.; Kim, S.; Bae, I.G. Successful control of carbapenem-resistant *Acinetobacter baumannii* in a Korean university hospital: A 6-year perspective. *Am. J. Infect. Control* 2014, 42, 976–979. [CrossRef] [PubMed]

27. Munoz-Price, L.S.; Carling, P.; Cleary, T.; Fajardo-Aquino, Y.; DePascale, D.; Jimenez, A.; Hughes, M.; Namias, N.; Pizano, L.; Kett, D.H.; et al. Control of a two-decade endemic situation with carbapenem-resistant *Acinetobacter baumannii*: Electronic dissemination of a bundle of interventions. *Am. J. Infect. Control* 2014, 42, 466–471. [CrossRef]

28. Valencia-Martin, R.; Gonzalez-Galan, V.; Alvarez-Marin, R.; Cazalla-Foncuvea, A.M.; Aldabó, T.; Gil-Navarro, M.V.; Alonso-Araujo, I.; Martin, C.; Gordon, R.; Garcia-Nuñez, E.J.; et al. A multimodal intervention program to control a long-term *Acinetobacter baumannii* endemic in a tertiary care hospital. *Antimicrob. Resist. Infect. Control* 2019, 8, 199. [CrossRef] [PubMed]

29. Enfield, K.B.; Huq, N.N.; Gosseling, M.F.; Low, D.J.; Hazen, K.C.; Toney, D.M.; Slitt, G.; Zapata, H.J.; Cox, H.L.; Lewis, J.D.; et al. Control of Simultaneous Outbreaks of Carbapenemase-Producing Enterobacteriaceae and Extensively Drug-Resistant *Acinetobacter baumannii* Infection in an Intensive Care Unit Using Interventions Promoted in the Centers for Disease Control and Prevention 2012 Carbapenem-Resistant Enterobacteriaceae Toolkit. *Infect. Control Hosp. Epidemiol.* 2014, 35, 810–817. [CrossRef] [PubMed]

30. Karampatakis, T.; Tsergouli, K.; Iosifidis, E.; Antachopoulos, C.; Karapanagiotou, A.; Karyoti, A.; Gritsi-Gerogianni, N.; Tsakris, A.; Rosildes, E. Impact of active surveillance and infection control measures on carbapenem-resistant Gram-negative bacterial colonization and infections in intensive care. *J. Hosp. Infect.* 2018, 99, 396–404. [CrossRef] [PubMed]

31. Eckardt, P.; Canavan, K.; Guran, R.; George, E.; Miller, N.; Himed, K.; Ramirez, K.H.G. Containment of a carbapenem-resistant *Acinetobacter baumannii* complex outbreak in a COVID-19 intensive care unit. *Am. J. Infect. Control* 2022, 50, 477–481. [CrossRef] [PubMed]

32. Chung, Y.K.; Kim, J.S.; Lee, S.S.; Lee, J.A.; Kim, H.S.; Shin, K.-S.; Park, E.Y.; Kang, B.S.; Lee, H.J.; Kang, H.J. Effect of daily chlorhexidine bathing on acquisition of carbapenem-resistant *Acinetobacter baumannii* (CRAB) in the medical intensive care unit with CRAB endemicity. *Am. J. Infect. Control* 2015, 43, 1171–1177. [CrossRef] [PubMed]

33. Meschiari, M.; López-Lozano, J.M.; Di Pilato, V.; Gimenez-Esparza, C.; Vecchi, E.; Bacca, E.; Orlando, G.; Franceschini, E.; Sarti, M.; Pecorari, M.; et al. A five-component infection control bundle to permanently eliminate a carbapenem-resistant *Acinetobacter baumannii* spreading in an intensive care unit. *Antimicrob. Resist. Infect. Control* 2021, 10, 123. [CrossRef]

34. Zhao, Y.; Hu, K.; Zhang, J.; Guo, Y.; Fan, X.; Wang, Y.; Mensah, S.D.; Zhang, X. Outbreak of carbapenem-resistant *Acinetobacter baumannii* carrying the carbapenemase OXA-23 in ICU of the eastern Heilongjiang Province, China. *BMC Infect. Dis.* 2019, 19, 452, Erratum in *BMC Infect. Dis.* 2019, 19, 621. [CrossRef] [PubMed]

35. Ben-Cherit, E.; Wiener-Well, Y.; Lesho, E.; Kopuit, P.; Broyer, C.; Bier, L.; Assous, M.V.; Benenson, S.; Cohen, M.J.; McGann, P.T.; et al. An intervention to control an ICU outbreak of carbapenem-resistant *Acinetobacter baumannii*: Long-term impact for the ICU and hospital. *Crit. Care* 2018, 22, 319. [CrossRef] [PubMed]

36. Metan, G.; Zarakolu, P.; Oltu, B.; Tekin, I.; Aytaç, H.; Böle, E.Ç.; Metin, B.Ç.; Arsava, E.M.; Ünal, S. Emergence of colistin- and carbapenem-resistant Acinetobacter calcoaceticus-*Acinetobacter baumannii* (CCR-Acb) complex in a neurological intensive care unit followed by successful control of the outbreak. *J. Infect. Public Health* 2020, 13, 564–570. [CrossRef] [PubMed]

37. Oldenkamp, R.; Schultz, C.; Mancini, E.; Cappuccio, A. Filling the gaps in the global prevalence map of clinical antimicrobial resistance. *Proc. Natl. Acad. Sci. USA* 2021, 118, e2013515118, Erratum in *Proc. Natl. Acad. Sci. USA* 2021, 118, e2116827118. [CrossRef] [PubMed]

38. The Center for Disease Dynamics, Economics & Policy. ResistanceMap: [Resistance of *Acinetobacter baumannii* to Carbapenems]. 2022. Available online: https://resistancemap.cddep.org/AntibioticResistance.php (accessed on 23 May 2022).

39. European Centre for Disease Prevention and Control. *Carbapenem-Resistant Acinetobacter baumannii Related to Recent Hospitalisation in Ukraine*; European Centre for Disease Prevention and Control: Stockholm, Sweden, 2022.

40. World Health Organization. *Guidelines on Core Components of Infection Prevention and Control Programmes at the National and Acute Health Care Facility Level*; World Health Organization: Geneva, Switzerland, 2016. Available online: https://apps.who.int/iris/handle/10665/251730 (accessed on 6 June 2022).
41. Association for Professionals in Infection Control and Epidemiology (APIC). *Guide to the Elimination of Multidrug-Resistant Acinetobacter baumannii Transmission in Healthcare Settings;* Association for Professionals in Infection Control and Epidemiology: Washington, DC, USA, 2010.

42. World Health Organization. *Hand Hygiene Technical Reference Manual;* World Health Organization: Geneva, Switzerland, 2009. Available online: https://apps.who.int/iris/handle/10665/44196 (accessed on 12 June 2022).

43. Anderson, D.J.; Chen, L.F.; Weber, D.J.; Moehring, R.W.; Lewis, S.S.; Triplett, P.F.; Blocker, M.; Becherer, P.; Schwab, J.C.; Knelson, L.P.; et al. Enhanced terminal room disinfection and acquisition and infection caused by multidrug-resistant organisms and *Clostridium difficile* (the Benefits of Enhanced Terminal Room Disinfection study): A cluster-randomised, multicentre, crossover study. *Lancet* 2017, 389, 805–814. [CrossRef]

44. Anderson, D.J.; Knelson, L.P.; Moehring, R.W.; Lewis, S.S.; Weber, D.J.; Chen, L.F.; Triplett, P.F.; Blocker, M.; Cooney, R.M.; Schwab, J.C.; et al. Implementation Lessons Learned from the Benefits of Enhanced Terminal Room (BETR) Disinfection Study: Process and Perceptions of Enhanced Disinfection with Ultraviolet Disinfection Devices. *Infect. Control Hosp. Epidemiol.* 2018, 39, 157–163. [CrossRef] [PubMed]

45. Dancer, S.J.; King, M.F. Systematic review on use, cost and clinical efficacy of automated decontamination devices. *Antimicrob. Resist. Infect. Control* 2021, 10, 34. [CrossRef]

46. Fan, C.Y.; Lee, W.T.; Hsu, T.C.; Lee, C.H.; Wang, S.P.; Chen, W.S.; Huang, C.H.; Lee, C.C. Effect of chlorhexidine bathing on colonization or infection with *Acinetobacter baumannii*: A systematic review and meta-analysis. *J. Hosp. Infect.* 2019, 103, 284–292. [CrossRef] [PubMed]

47. Rizk, N.A.; Zahreddine, N.; Haddad, N.; Ahmadieh, R.; Hannun, A.; Bou Harb, S.; Haddad, S.F.; Zeenny, R.M.; Kanj, S.S. The Impact of Antimicrobial Stewardship and Infection Control Interventions on *Acinetobacter baumannii* Resistance Rates in the ICU of a Tertiary Care Center in Lebanon. *Antibiotics* 2022, 11, 911. [CrossRef]