Carbapenem-resistant Acinetobacter baumannii: A challenge in the intensive care unit

Yuan Jiang, Yinhuan Ding, Yueshuai Wei, Chunxia Jian, Jinbo Liu*† and Zhangrui Zeng*†

Department of Laboratory Medicine, The Affiliated Hospital of Southwest Medical University, Luzhou, China

Carbapenem-resistant Acinetobacter baumannii (CRAB) has become one of the leading causes of healthcare-associated infections globally, particularly in intensive care units (ICUs). Cross-transmission of microorganisms between patients and the hospital environment may play a crucial role in ICU-acquired CRAB colonization and infection. The control and treatment of CRAB infection in ICUs have been recognized as a global challenge because of its multiple-drug resistance. The main concern is that CRAB infections can be disastrous for ICU patients if currently existing limited therapeutic alternatives fail in the future. Therefore, the colonization, infection, transmission, and resistance mechanisms of CRAB in ICUs need to be systematically studied. To provide a basis for prevention and control countermeasures for CRAB infection in ICUs, we present an overview of research on CRAB in ICUs, summarize clinical infections and environmental reservoirs, discuss the drug resistance mechanism and homology of CRAB in ICUs, and evaluate contemporary treatment and control strategies.

KEYWORDS

carbapenem-resistant Acinetobacter baumannii, intensive care unit, infection, environmental contamination, resistance mechanism, homology, treatment and control strategies

Introduction

The incidence of drug-resistant organism infection is currently increasing in hospitals and other clinical care settings, particularly in ICUs. A place that provides life support for critically ill or unconscious patients, ICU is the cornerstone of life extension for critically ill patients. However, because of a delayed immune response, reduced host defense, and use of invasive devices—central venous catheterizations, mechanical ventilation, and urinary tract catheterizations—patients in ICUs have an increased risk of infection. The morbidity and mortality of such infections have been reduced by the extensive use of antibiotics in recent decades. However, with the rise of the use of antibiotics in the treatment of microbial infections, increased selection pressures promote the emergence and dissemination of
drug-resistant pathogens (Lipsitch and Samore, 2002; Esposito and Leone, 2007; Baker et al., 2018).

A significant positive association between antibiotic resistance rates and antibiotic consumption has been determined, together with a rising trend in antimicrobial resistance (Agodi et al., 2015). Carbapenems were once recognized as a pillar of treatment for clinical critical infections, but with their widespread use, resistance to carbapenems has increased as well. The emergence and dissemination of carbapenem-resistant non-fermenting Gram-negative bacilli (NFGNB) in ICUs pose a substantial threat in hospitals (Agarwal et al., 2017; Kousouli et al., 2019). Among these bacteria, CRAB is increasingly becoming one of the leading causes of healthcare-associated infections (HAIs), particularly in ICUs (Blanco et al., 2018; Busani et al., 2019; Chen et al., 2019; Tomczyk et al., 2019). In the Global Priority List of Antibiotic-Resistant Bacteria published by the World Health Organization (WHO) in 2017, CRAB was classified as among those bacteria for which antibiotics are most urgently needed (Tacconelli et al., 2018).

CRAB has been associated primarily with respiratory tract infections in ICUs, particularly ventilator-associated pneumonia (VAP; Nhu et al., 2014; Karruli et al., 2021; Khalil et al., 2021; Said et al., 2021; Pogue et al., 2022). Although no definitive agreement has been reached on the links between CRAB infections and an increased risk of mortality, CRAB infections have exhibited a significant association with the length of ICU stay, increased patient costs, and antibiotic use (Phu et al., 2017; Kousouli et al., 2019; Zhen et al., 2020; Liu Y. et al., 2020; Ejaz et al., 2021). Polymyxin currently remains effective as a treatment method for CRAB infections in ICUs (Garnacho-Montero et al., 2015; Sana et al., 2021). However, on an individual-patient basis, the use of polymyxin remains rather limited because of nephrotoxicity and neurotoxicity (Nazer et al., 2015b; Katip and Oberdorfer, 2021; Liu et al., 2021; Zhang N. et al., 2021). The emergence of polymyxin resistance in A. baumannii has also been reported (Cheah et al., 2016a,b; Carrasco et al., 2021). Under these conditions, the control and treatment of CRAB in ICUs can potentially face new challenges and have prompted growing concern in the medical community.

Therefore, evidence-based interventions to strengthen prevention and control initiatives are urgently needed. Funding, research, and development of new antimicrobials should pay increased attention to CRAB infections in ICUs. This review focuses on CRAB infections in ICUs and its transmission, mechanisms of resistance, treatment alternatives, and control strategies to provide a basis for prevention and control countermeasures for CRAB infections in ICUs.

**CRAB in ICUs**

**CRAB infections of patients in ICUs**

WHO estimates that about 30% of ICU patients are affected by at least one HAI in high-income countries; meanwhile, the frequency is at least two-fold to three-fold higher in middle- and low-income countries (World Health Organization, 2011). NFGNB is the leading cause of HAI, among which A. baumannii is an opportunistic pathogen that causes hospital-acquired septicemia, pneumonia, and urinary tract infections, particularly in ICUs (Antunes et al., 2014; Harding et al., 2018). Notably, as CRAB isolates in growing numbers have been isolated from patients, the prevalence and risk factors of CRAB infections have received increasing attention.

VAP, a severe complication, remains to be the most common infection acquired in ICUs (Kalanuria et al., 2014; Kalil et al., 2016). The pathogens responsible for VAP and their resistance mechanisms in ICUs are difficult to identify. The emergence and popularity of CRAB, which causes pulmonary infection in ICUs, have been reported in numerous publications. One multicenter prospective study found that multidrug-resistant Gram-negative bacteria, including A. baumannii, K. pneumoniae, and P. aeruginosa, are frequently associated with VAP in ICUs (Bandić-Pavlović et al., 2020). In a study conducted over a period of 46 months, Lambiase et al. demonstrated that A. baumannii isolated from patients with VAP in ICUs were resistant to carbapenem with imipenem MIC ≥ 16 μg/ml (Lambiase et al., 2012).

A retrospective study further found that the sputum separation rate of CRAB from ICUs was markedly higher than those from non-ICUs, and the resistance rate of CRAB showed a significantly rising trend (He et al., 2020). Similarly, 80% of CRAB in ICUs were isolated from sputum specimens, and CRAB comprised more than 50% of carbapenem-resistant Gram-negative bacilli (Karuniawati et al., 2013; Łazureanu et al., 2016). Alternatively, another study showed that 58 of 61 A. baumannii isolates exhibited MICS with imipenem or meropenem ≥ 16 μg/ml, and pulmonary infection was the most common site (26 of 36 cases; Mammina et al., 2012). As is widely known, the use of mechanical ventilation is strongly associated with the incidence of VAP. Therefore, when lung infection due to CRAB occurs in ICUs, the use of ventilators should be paid more attention than other wards to prevent cross-infection. However, beyond the use of mechanical ventilation, independent risk factors for CRAB causing pulmonary infections have been identified, such as previous stays in other departments, longer ICU stay, and previous use of carbapenems (Nazer et al., 2015a; Djordjevic et al., 2016). That is to say, a comprehensive infection control strategy is required to effectively control the emergence and spread of CRAB in ICUs.

Zhou et al. reported that the high mortality associated with bloodstream infections (BSIs) caused by A. baumannii has become a major clinical concern (Zhou et al., 2019). As such, increased attention should be paid to patients with CRAB bacteraemia, apart from those with pulmonary CRAB infections. Invasive procedures and excessive use of antibiotics, particularly in patients with compromised immunity, are risk factors independently correlated with CRAB bacteraemia (Kim et al., 2012; Shirvohmamadiou et al., 2018). Previous studies have also found that colonization in
the respiratory tract and gastrointestinal tract by CRAB is a crucial step before nosocomial infection (Lazareva et al., 2014; Bado et al., 2018; Kiddee et al., 2018; Maamar et al., 2018). Identifying risk factors and providing targeted interventions may become effective approaches to reducing the incidence of CRAB-causing HAIs.

Environmental contamination of CRAB in ICUs

A. baumannii can persist in the environment for long-term periods. A. baumannii, which ubiquitously and continuously persists in the hospital setting is one of the main sources of HAIs (Sunenshine et al., 2007). Ng et al. reported that environmental CRAB contamination was detected in nearly two-thirds of the rooms housing patients with CRAB (Ng et al., 2018). Previous studies have also indicated that cross-contamination of multidrug-resistant bacteria, specifically CRAB in ICUs, may occur via the air (Shimose et al., 2016), high-density electroencephalogram material (Weiss et al., 2016), Velcro on blood pressure cuffs (Alfandari et al., 2014), medical devices, furniture, and gloves (Raro et al., 2017). Uwingabiye et al. also observed genetic similarity between environmental and clinical CRAB isolates in 96.4% of all isolates (Uwingabiye et al., 2017). Given the intersection between patients and the environment, increasing studies have been devoted to the study of the extensive environmental colonization of CRAB in ICUs.

CRAB from environmental (environment and healthcare workers from ICUs) and clinical samples has been isolated and analyzed in several studies (Royer et al., 2015; Raro et al., 2017; Jain et al., 2019; Al-Hamad et al., 2020; Liu W. et al., 2020; Wang et al., 2021), and it was found that the overwhelming majority of CRAB isolated from clinical and environmental samples produced OXA-23, but no clone was specifically responsible for both environmental colonization and ICU infections. However, the experimental results of pulsed-field gel electrophoresis (PFGE) have revealed the spread of carbapenem-resistant isolates via cross-transmission among the environment and patients (Royer et al., 2015; Jain et al., 2019). Similarly, Salehi et al. (2018) and Raro et al. (2017) analyzed the isolates of A. baumannii from patients, staff, and the environment, and emphasized the circulation of CRAB as a nosocomial pathogen in different wards of hospitals, particularly in ICUs. Shenoy et al. also identified highly contaminated areas and confirmed the role of environmental reservoirs by investigating five clinical CRAB infection cases (Shenoy et al., 2020). It should be noted that although environmental contamination of CRAB in ICUs has gained increasing attention, research about whether specific clone was responsible for both environmental colonization and ICU infections is still lacking.

Further, a prospective surveillance study for 8 months has shown that more than half of the CRAB strains originating from the air are clonally associated with the clinical strains of nine patients in two medical ICUs with 20 beds total (Yakupogullari et al., 2016). The results of this study (Yakupogullari et al., 2016) suggested that infected patients can spread CRAB in large quantities to the air of an ICU, and these strains can still infect new patients after several months. This conclusion was verified by another study in China (Jiang et al., 2018). That is to say, special infection control measures may be required to prevent the airborne spread of CRAB in ICUs.

Colonization is usually regarded as a fundamental ecological process. Bacterial colonization of the surfaces is almost ubiquitous, especially in healthcare settings. In addition, the colonization of gastrointestinal tract, respiratory tract, urinary tract, and axilla is also receiving growing interest from researchers. Previous studies have found that colonization is an essential step in pathogen infections (Chipolombwe et al., 2016; Weiser et al., 2018; Tanimoto et al., 2019). Besides, numerous studies have shown that colonization is an important risk factor for subsequent infection (Huang et al., 2006; Haber et al., 2007; Martin et al., 2016; Gorrie et al., 2017). Studying the relationship between colonization and infections may bring new insights into disease prevention and treatment.

Interestingly, several studies have found that air and environmental surface contamination of CRAB were significantly greater among patients with respiratory tract colonization and gastrointestinal colonization than in other types of patients (Rosa et al., 2014; Shimose et al., 2016). Moreover, in a retrospective cohort study, significant associations were observed between CRAB colonization and clinical infections (Latibeaudiere et al., 2015). Namely, respiratory tract colonization and gastrointestinal colonization also play prominent roles in CRAB infections in ICU patients. Meanwhile, the relationship between environmental contamination and pathogen infections also cannot be neglected in general wards (Al-Hamad et al., 2020). Overall, environmental reservoirs of CRAB play a pivotal role in the HAIs of CRAB. An intensive study of environmental CRAB is beneficial to the control and elimination of CRAB infections in ICUs. The figure below shows the transmission relationship of CRAB among patients, health care workers, and the environment in ICUs (Figure 1).

Drug resistance mechanism and homology of CRAB isolated from ICUs

The increase in drug-resistant bacterial infections leads to a heavy burden on healthcare systems globally. The study of drug resistance mechanisms is the first step to overcoming the infection of drug-resistant bacteria. CRAB has been classified by the WHO as one of the 12 top priority resistant bacteria presenting the most serious threat to public health (Tacconelli et al., 2018). As described previously, CRAB has been a major cause of HAIs (Sunenshine et al., 2007). Accordingly, a significant understanding of the mechanism underlying CRAB resistance is of major importance for drug development and clinical therapy.
An increasing number of researchers have conducted studies on drug resistance mechanisms and the homology of CRAB isolated from ICUs (Table 1). Details of the Table 1 reveal that most studies on the molecular characterization of CRAB in ICUs have been conducted in Asia and Africa, primarily in the developing world. Although the antibiotic resistance genes (ARGs) in the majority of studies have been dominated by \textit{bla}_{OXA-23-like}, differences in ARGs and CRAB molecular typing have been found between different countries and regions. These literature reviews reflect the high diversity of the ARGs of CRAB isolated from ICUs globally.

Zhang X. et al. (2021) investigated the phylogenetic relationships of 105 CRAB isolates from an ICU of a Chinese hospital and found that CRAB isolates contained 17 unique ARGs. And whole-genome sequencing (WGS) revealed the presence of \textit{bla}_{ADC-25}, \textit{bla}_{OXA-23}, and \textit{bla}_{NDM-1}, which belonged to Sequence type (ST) 2 (Zhang X. et al., 2021). A previous study indicated that carbapenem resistance was dominantly driven by the dissemination of CRAB isolates carrying \textit{bla}_{OXA-23} belonging to ST2 (Mahamat et al., 2016; Neves et al., 2016; Salehi et al., 2019). The \textit{bla}_{OXA-23} is mostly found on plasmids, and Corvec et al. (2007) found that \textit{IS}_{Aba1} and \textit{IS}_{Aba4} which were detected upstream of the \textit{bla}_{OXA-23} gene, provided promoter sequences for its expression.

In addition to \textit{bla}_{OXA-23}, ARGs such as \textit{bla}_{OXA-24/40}, \textit{bla}_{OXA-51}, \textit{bla}_{OXA-58}, and \textit{bla}_{OXA-72} also play prominent roles in the drug resistance of CRAB (Schultz et al., 2016; Mavroidi et al., 2017; Chen et al., 2018b; Salehi et al., 2019; Zhang Y. et al., 2021). The \textit{bla}_{OXA-24-like} genes have been identified as chromosomally encoded. And Azizi et al. found that the isolates of \textit{A. baumannii} with both \textit{bla}_{OXA-23} and \textit{bla}_{OXA-24} had strong biofilm-forming capability (Azizi et al., 2015). It is well known that biofilms can facilitate the development of antibiotic resistance by limiting bacterial exposure to antibiotics. Apart from the aforementioned genes, biofilms and AdeABC efflux-pump genes have also been detected in CRAB isolated from ICUs (Mavroidi et al., 2017; Chen et al., 2018a; Khalil et al., 2019).
TABLE 1  Studies on CRAB and its ARGs isolated from ICU patients.

| Country | References | Period of study | Number of CRAB | Wards | ARGs                                                                 | Molecular Typing |
|---------|------------|-----------------|----------------|-------|----------------------------------------------------------------------|------------------|
| Tunisia | Maamar et al. (2018) | Dec 2014 to Feb 2015 | 13 | ICU | blaOXA-23 (84.6%), blaOXA-24 (15.4%), armA (84.6%), tetB (84.6%), sul1 (84.6%), catB (84.6%), aph(3')-Vla (69.2%), aph(3')-lai (15.4%), ant(2')-lai (15.4%), blaOXA-40 (30.8%) | ST195 (84.6%), ST1089 (15.4%) |
| Egypt  | Ramadan et al. (2018) | Jul 2017 to Dec 2017 | 30 | ICU | blaOXA-23 (90%), blaOXA-24 (66.7%), blaOXA-23 (50%) | Unknown |
| Uganda | Aruhomukama et al. (2019) | Jan 2015 to Dec 2017 | 21 | ICU (16), Other wards (5) | blaVIM (100%), blaVIM + class 1 integron (61.9%), blaOXA-23 (29%), blaOXA-24 (24%), blaOXA-51 (100%) | Unknown |
| Egypt  | Khalil et al. (2021) | May 2019 to Feb 2021 | 54 | ICU | blaOXA-23-like (88.9%), blaOXA-24 (9.2%), Bap (25.9%), blaOXA-51 (11.1%) | REP-PCR Genotyping: four distinctive REP-PCR clusters (A-D) and two (746A, 715A) singleton isolates |
| Nigeria | Odih et al. (2022) | Aug 2017 to Jun 2018 | 34 | ICU | blaOXA-23 (100%), blaOXA-24 (50%), blaOXA-23 (44.1%), blaOXA-24 (5.9%), sul1 (29.4%), sul2 (29.4%) | ST2 (29.4%), ST85 (23.5%), ST149 (8.8%), ST25 (5.8%), ST164 (5.9%), other STs (17.6%) |
| China  | Zhao et al. (2019) | Jan 2010 to Dec 2017 | 21 | ICU | blaOXA-23 (100%), blaOXA-24 (28.6%), blaOXA-23 (100%), blaOXA-24 (100%), blaOXA-23 (95.2%), ISAba1 (95.2%), ISA-23 (95.2%), ISA-ADC (28.6%) | ST2 (95.2%), ST1119 (4.8%) |
| China  | Qian et al. (2015) | Jan 2010 to Jan 2014 | 140 | ICU (48), Respiration Medicine (49), Burn and Plastic Surgery (43) | blaOXA-23 (93.3%), blaOXA-24 (6.7%), sul1 (6.1%), imp (12.3%), mtrF (57.9%), qacEt1-sul1 (61.2%) | ST208 (52.1%), ST218 (47.9%) |
| China  | Zhang et al. (2021c) | Jul 2018 to Jun 2019 | 91 | ICU | blaOXA-23 (100%), blaOXA-23 (93.4%), blaOXA-23 (2.2%), blaOXA-23 (2.2%), ISAba1/blaOXA-23 (27.5%), blaOXA-23 (8.8%) | Unknown |
| China  | Wang et al. (2021) | Jul 2017 to Dec 2017 | 61 | ICU | blaOXA-23 (100%), blaOXA-23 (100%), blaOXA-23 (100%), gyrA mutation (95.1%) | ST208 (93.5%), ST369 (1.6%), ST373 (4.9%) |
| China  | Zhang et al. (2021b) | Jan 2013 to Dec 2018 | 105 | ICU | blaOXA-23 (100%), blaOXA-24 (100%), blaOXA-23 (100%), blaOXA-24 (81.9%), aac(6')-Ib (15.2%), aac(6')-Ib-cr (15.2%), aph(3')-Ls (16.2%), aph(3')-Ls (81.0%), aph(6')-Ia (83.8%), armA (97.1%), aadA (83.8%), mph(E) (97.1%), msr(E) (97.1%), catB8 (97.1%), tetB (83.8%), sul1 (16.2%), sul2 (44.8%) | ST2 (100%) |

(Continued)
TABLE 1 (Continued)  

| Country   | References                      | Period of study          | Number of CRAB | Wards                  | ARGs                                       | Molecular Typing |
|-----------|---------------------------------|--------------------------|----------------|------------------------|--------------------------------------------|------------------|
| China     | Chen et al. (2018b)             | Jan 2014 to Dec 2016     | 78             | ICU (51) Other wards (27) | bla \(\text{OXA-51}\) (100%), \(\text{OXA-23}\) (57.7%), \(\text{OXA-51/58}\) (42.3%), \(\text{OXA-23/51/58}\) (1.3%) | ST2 (100%)       |
| China     | Zhou et al. (2015)              | May 2012 to Nov 2013     | 46             | ICU                    | \(\text{OXA-51}\) (100%), \(\text{OXA-23}\) (100%), \(\text{OXA-51}\) + ISAb1 (84.8%) | ST195 (54.4%), ST365 (19.3%), ST92 (8.8%), ST381 (5.3%), ST75 (1.8%), five novel ST isolates (10.7%) |
| China     | Liu and Liu (2021)              | Jul 2019 to Jan 2020     | 60             | ICU (30) Respiratory Department (30) | \(\text{OXA-23}\) (80%), \(\text{VIM-2}\) (23.3%), \(\text{IMP-4}\) (40%), \(\text{NDM-1}\) (20%), \(\text{ampC}\) (16.7%), mutation of CarO (86.7%) | ST450 (36.6%), ST195 (22.0%), ST208 (18.3%), ST191 (13.4%), ST369 (4.9%), ST469 (2.4%), ST381 (1.2%), ST36 (1.2%) |
| China     | Guo and Li (2019)               | Jan 2017 to Jan 2018     | 82             | ICU                    | \(\text{OXA-51}\) (100%), \(\text{OXA-23}\) (100%), \(\text{qac}\) (76.8%), \(\text{qacE}\) (30.5%) | ST540 (36.6%), ST195 (22.0%), ST208 (18.3%), ST191 (13.4%), ST369 (4.9%), ST469 (2.4%), ST381 (1.2%), ST36 (1.2%) |
| Pakistan  | Ejaz et al. (2021)              | Sep 2020 to Dec 2020     | 113            | ICU (81) Other wards (32) | \(\text{OXA-23}\) (89%), \(\text{OXA-24}\) (29%), \(\text{OXA-143}\) (100%), \(\text{qac}\) (2.4%), \(\text{qacG}\) (6.7%), \(\text{qacE}\) (4.1%) | ST2 (46.9%), ST1 (15.9%), ST589 (12.3%), ST7 (9.7%), ST158 (8.8%), ST23 (4.4%), ST25 (1.7%) |
| Iran      | Shirmohammadlou et al. (2018)   | Jun 2014 to Mar 2016     | 100            | ICU                    | \(\text{OXA-51}\) (89%), \(\text{OXA-23}\) (29%), \(\text{OXA-143}\) (100%), \(\text{qac}\) (6.7%), \(\text{qacG}\) (4.1%) | Unknown |
| Iran      | Salehi et al. (2019)            | Aug 2016 to Feb 2017     | 180            | ICU (134) Other wards (46) | \(\text{OXA-23}\) (60.5%), \(\text{OXA-24}\) (17.2%), \(\text{OXA-58}\) (17.2%), | Unknown |
| Thailand  | Kiddee et al. (2018)            | Dec 2014 to Dec 2015     | 43             | ICU                    | \(\text{OXA-23}\) (2.3%), \(\text{OXA-24}\) (2.3%), \(\text{OXA-143}\) (4.7%), \(\text{OXA-23}\) (2.3%), \(\text{OXA-23}\) (14.0%), \(\text{OXA-23}\) (46.5%), \(\text{OXA-23}\) (9.3%), \(\text{OXA-23}\) (11.6%), | Unknown |
| Croatia   | Bandić-Pavlović et al. (2020)  | Sep 2017 to Mar 2018     | 23             | ICU                    | \(\text{AmpC}\) (100%), \(\text{OXA-23}\) (34.8%), \(\text{OXA-23}\) (52.2%) | ST1 (13.0%), ST2 (87.0%) |
| Italy     | Mammina et al. (2012)           | Oct 2010 to Mar 2011     | 61             | ICU                    | \(\text{OXA-23}\) (100%), \(\text{OXA-23}\) (80.3%), \(\text{OXA-23}\) (3.3%) | ST2 (96.7%), ST78 (3.3%) |
| Italy     | Mezzatesta et al. (2014)        | Jan 2013 to Jul 2013     | 52             | ICU                    | \(\text{OXA-23}\) (100%), \(\text{OXA-23}\) (100%) | ST2 (100%)       |
| Italy     | Venditti et al. (2019)          | Dec 2016 to Apr 2017     | 13             | ICU (12) Other wards (1) | \(\text{OXA-23}\) (100%), \(\text{OXA-23}\) (100%) | ST2 (100%)       |
| Brazil    | Neves et al. (2016)             | Dec 2009 to Dec 2010     | 56             | ICU                    | \(\text{OXA-23}\) (100%), \(\text{OXA-23}\) (51.2%), \(\text{OXA-23}\) (18.6%) | Unknown |
| Uruguay   | Bado et al. (2018)              | Aug 2010 to Jul 2011     | 78             | ICU                    | \(\text{OXA-23}\) (100%), \(\text{OXA-23}\) (79.5%), \(\text{OXA-23}\) (3.8%) | ST79 (95.5%), ST958 (4.5%) |
2021). However, there are relatively few studies on biofilms and efflux-pump of CRAB in ICUs. It seems highly likely that the biofilms and efflux-pump of CRAB have not gained enough attention in ICUs.

The emergence of CRAB may be promoted by the adaptation and dissemination of a diverse group of successful clones. In a retrospective study of the drug resistance and distribution of pathogens isolated from the ICUs of 12 hospitals, Liu et al. found homology in the PFGE typing of CRAB (Liu W. et al., 2020). Moreover, Salehi et al. demonstrated that nine cross-existing clones consisting of eight cluster types and one ST were present between two hospitals (Salehi et al., 2019). Likewise, in South Africa, a study involving two hospitals found that ST106, ST229, ST258, and ST208 were established in both hospitals; meanwhile, ST339, ST502, and the novel ST1552 were established in Hospital B only, whereas ST848 was established in Hospital A only (Lowe et al., 2018). ST2 was identified as the most predominant isolate in Italy in several studies (Mammina et al., 2012; Mezzatesta et al., 2014; Schultz et al., 2016). It seems quite different from the distribution in other areas. In addition, resistance mechanisms and molecular epidemiology in the CRAB isolates varied between the general wards and ICUs. This result is supported by the PCR detection results of resistance genes, PFGE, and multilocus sequence typing (MLST) analysis in a recent study (Liu and Liu, 2021). The diverse ST types in different countries and regions have been listed in Table 1. Although CRAB infections have been reported all over the world, the lack of reports of molecular characterization targeted CRAB in ICUs is noticeable in some regions. Thus, further studies are needed to provide further evidence.

Overall, despite a certain degree of homology in CRAB from different ICUs, a high genetic diversity could not be overlooked. Further studies and investigations on the homology and drug resistance mechanism of CRAB in ICUs have important implications for reversing and reducing drug resistance, as well as developing control and treatment strategies.

### Strategies and advice

#### Treatment strategies for CRAB infections

**Guidelines for the treatment of CRAB infections**

As previously mentioned, CRAB infections have become increasingly prevalent worldwide. The increasing healthcare burden caused by CRAB in ICUs has directed widespread attention to the treatment and control of CRAB. However, limited therapeutic options, as well as the long study period and task difficulty involved in new drug development, have prompted the increased interest among researchers devoting themselves to evaluating and improving treatment regimens on the basis of existing drugs. As clinical treatment options continued to be evaluated and studied, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) set guidelines in 2021 for the treatment of multidrug-resistant Gram-negative bacilli infections (Paul et al., 2022). The Infectious Diseases Society of America (IDSA) also recently updated the guidance document on the treatment of AmpC ß-lactamase-producing Enterobacterales, CRAB, and infections caused by *Stenotrophomonas maltophilia* (Tamma et al., 2022). Both guidelines include therapeutic choices for CRAB infections. Subtle differences between these two guidance documents are observed despite the similarity of the majority of treatment strategies for CRAB. The current study presents a summary in Figure 2.

In addition to the two guidelines by IDSA and ESCMID, similar guidelines including the treatment strategies related to CRAB infections have also been published in other regions and countries, such as China, Italy, and Arab countries of the Middle East (Guan et al., 2016; Al Salman et al., 2020; Tiseo et al., 2022). These recommendations present the distribution of diverse social and healthcare structures of different regions, as well as compensates for the deficiencies of international consensus guidelines. It is worth noting that, Table 1 lists China, Italy, and Arab countries of the Middle East as the main regions reporting CRAB infections in ICUs. In the consensus statement in Arab countries of the Middle East, *A. baumannii* infections are divided into two parts: (1) bacteremia and nosocomial pneumonia; (2) complicated urinary tract infection, and complicated skin and soft tissue infection. The treatment schemes, including first-choice therapy and duration, can vary based on the type of infection (Al Salman et al., 2020). In addition, three recommendations are presented in the guidance document in Italy with the following brief overview: (1) Consultation with specialists is recommended; (2) Rigorous monitoring of renal function is strongly recommended when colistin is administered; (3) Although ceftedicol represents a high-potential alternative for patients with CRAB infections, further studies need to be conducted to estimate the use of ceftedicol (Tiseo et al., 2022). In 2016, the Chinese consensus statement on the antimicrobial treatment of extensively drug-resistant Gram-negative bacilli (XDR-GNB) infections was released (Guan et al., 2016). This statement included the treatment strategies of XDR-GNB and was regarded as a reference for the treatment of CRAB infections. In 2019, the recommendations for antimicrobial treatment of CRAB infections were explicitly proposed in “Technical Guidelines for Prevention and Control of Carbapenem-resistant Gram-Negative Bacilli Infection in China” (Hu, 2019). An overview of these three guidelines is presented in Table 2 for a more intuitive comparison. The Table 2 shows that compared with the guidelines in Arab countries of the Middle East and China, the guidance document in Italy contains no detailed treatment strategies. Medical institutions in Italy were likely to comply with the guideline-recommended treatment strategies in ESCMID.
In summary, although many regions have proposed treatment guidelines and consensus on CRAB, the recommendations for the antimicrobial treatment of CRAB infections differed widely among different areas on the basis of the variations in antimicrobial availability, local preferences, and resistance patterns. Moreover, these recommendations need to be updated periodically in accordance to the evolution and spread of antibiotic resistance, and the advent of novel therapeutic strategies.

Other studies for treatment strategies

Despite the growing availability of guidelines, numerous questions about the treatment of CRAB infections arise. Ehrentraut et al. found that the use of colistin without drug concentration monitoring might be unsafe for critically ill patients, and treatment in accordance with guidelines does not ensure efficient target levels (Ehrentraut et al., 2020). The high frequency of isolation of CRAB in ICUs requires accurate antimicrobial susceptibility testing (AST), particularly to colistin, to ensure treatment precision (Sacco et al., 2021). Accordingly, drug concentration monitoring and the accurate application of AST are indispensable when treating with colistin; in addition, the safety assessment of colistin monotherapy requires further study. Moreover, in treating the BSIs of carbapenem-resistant NFGNB, high-dosage tigecycline (TGC) therapy was not superior to standard TGC dosing, and TGC-based combination antimicrobial therapy was not superior to monotherapy (Qu et al., 2021). Thus, whether TGC is suitable for the treatment of CRAB infections requires further research and verification.
In addition to the treatment alternatives included in these guidelines, other treatment strategies have also been recently examined in response to the development of antibiotic resistance. Phage therapy is regarded as a promising selection for treating pulmonary bacterial infections. Wu et al. reported that using a pre-optimized two-phage cocktail in ICUs can cause a significant decrease in CRAB burden (Wu et al., 2021). Other treatment strategies in recent years also included N-acetylcysteine plus antibiotics (Oliva et al., 2021), trimethoprim–sulfamethoxazole (Raz-Pasteur et al., 2019), and other sulbactam-based combinations (Qu et al., 2020). These therapeutic strategies may be further studied in the future. However, integrated strategies for the effective prevention and control of infection caused by drug-resistant bacteria have to be urgently developed because of the evolution and spread of antibiotic resistance, as well as existing challenges and limitations in pharmaceutical research.

### Infection control strategies

Awareness of infection prevention and control has increased with intensified research in epidemiology. Agodi et al. indicated that infection control measures are equally important as the cautious use of antibiotics (Agodi et al., 2015). In 2017, WHO published the first global guidelines for the prevention and control of carbapenem-resistant *Enterobacteriaceae–A. baumannii–P. aeruginosa* in health care facilities, including eight evidence-based recommendations distilled by leading global experts (World Health Organization, 2017). Subsequently, the WHO global report on infection prevention and control provided a global situation analysis for policymakers at different levels, which can be used to facilitate the development of disease control strategies (World Health Organization, 2022). Accordingly, a growing number of healthcare workers have devoted themselves to the prevention and control of drug-resistant bacteria infections in ICUs. Thus, measures taken for CRAB infection control in ICUs are further discussed in the succeeding section.

### Control of carbapenem use

The emergence, persistence, and dissemination of CRAB in ICUs limit therapeutic efficacy in critically ill patients. Antibiotic resistance is an ancient natural mechanism (Munita and Arias, 2016), but recent antibiotic usage effectively imposes selection pressure on ARGs. Selection pressure due to the use of antibiotics leads to the emergence, persistence, and dissemination of clinical resistant strains. Up to half of antibiotic courses might be inappropriate for use in ICUs (Barnes et al., 2017). Short-term carbapenem restriction effectively reduces the incidence of CRAB in ICUs (Ogutlu et al., 2014; Abdallah et al., 2019). Further, Munoz-Price et al. reported that every additive carbapenem-defined daily dose increased the risk of CRAB by 5.1% (Munoz-Price et al., 2016). Djordjevic et al. showed that previous use of carbapenems was a risk factor for CRAB infections in ICUs, and also demonstrated that appropriate policy of antibiotic utilization was an important measure that may decrease the incidence of such infections (Djordjevic et al., 2016). Therefore, controlling the usage of carbapenems to a certain degree can reduce the emergence and spread of CRAB in ICUs. However, the inevitable use of carbapenems prompts...
the need for stronger evidence to support and guide the use of antibiotics.

**Early epidemiological screening for CRAB**

As described previously (2.1), colonization by CRAB is a crucial step before nosocomial infection. Patients with CRAB intestinal colonization are more likely to develop CRAB infections, and admission screening of fecal carriage can prevent its spread (Maamar et al., 2018; Qiao et al., 2020). Culture processes and polymerase chain reaction (PCR) have long been regarded as the most common means of epidemiological screening for pathogens. Technological advancements have led to the development of new techniques to assist clinicians in early epidemiological screening for pathogens.

Investigators have detected *A. baumannii* and carbapenem resistance by loop-mediated isothermal amplification (LAMP) assay and found that LAMP was expected to act as an effective mean for early detection (Garciglia-Mercado et al., 2021; Sharma and Gaind, 2021). Rapid screening using LAMP assay followed by early intervention has also been reported to potentially decrease the transmission rates of CRAB in ICUs (Yamamoto et al., 2019). Li et al. optimized and evaluated the LAMP method, and their results showed that in *A. baumannii* detection, the sensitivity of LAMP was tenfold higher than that of PCR (Li et al., 2015). Garciglia-Mercado et al. reached a similar conclusion (Garciglia-Mercado et al., 2020). In addition to the LAMP assay, WGS was a valuable tool in epidemiological studies (Venditti et al., 2019). However, although the cost of sequencing has significantly decreased in recent years, WGS in epidemiological investigations remains extremely costly. Therefore, LAMP can potentially be used as an available screening method in epidemiologic investigations of CRAB, balancing sensitivity with the cost of detection.

**Interventions**

On the basis of the screening results, adequate control and disinfection measures can effectively limit the transmission of CRAB in ICUs. Chung et al. observed a 51.8% reduction in CRAB infection rates after daily chlorhexidine bathing in ICUs with CRAB endemcity (Chung et al., 2015). Other studies also indicated that daily bathing with 2% chlorhexidine gluconate can reduce CRAB cross-transmission among patients in ICUs with high CRAB endemcity (Hong et al., 2018; Metan et al., 2020; Suh et al., 2021). Moreover, environmental cleaning, isolation, and enhanced contact precautions are also integrated into strategies preventing CRAB cross-transmission among patients in ICUs because of the environmental reservoirs of CRAB.

Numerous studies have devoted themselves to preventing and addressing the environmental contamination and cross-transmission of CRAB in ICUs in recent years (Karampatakis et al., 2020; Dickstein et al., 2021; Jung et al., 2021; Kelly et al., 2021). First, the most significant point is that healthcare personnel education should be promoted to strengthen awareness and preparedness. Karampatakis et al. associated the increased infection rates for CRAB with work programs and behavioral factors (Karampatakis et al., 2020). Similarly, Kousouli et al. identified reduced compliance with hand hygiene and participation in educational courses as the most significant factor for CRAB bloodstream infection (Kousouli et al., 2018). A study in China found that after targeted surveillance, further implementation of infection control, including staff education, hand hygiene, and environmental cleaning can effectively prevent the spread of nosocomial CRAB infections (Zhao et al., 2019).

Second, new admissions should be separated from patients with colonization and infection, and their treatment should be handled by different medical staff members. An et al. isolated and grouped patients by CRAB culture results. They observed that the rate of CRAB infections and the use of colistin significantly decreased during the study period (An et al., 2017). Further, single-person isolation in ICUs was found to be an efficient method to prevent the transmission and hospital-acquired infections of CRAB (Guth et al., 2016; Jung et al., 2021).

Third, adequate environmental cleaning and disinfection also decrease the risk of transmission and infection of CRAB. Ben-Chetrit et al. showed that after environmental cleaning and hand hygiene, CRAB acquisition in ICUs considerably decreased from 54.6 to 1.9 (year 1) and 5.6 cases (year 2)/1,000 admissions (Ben-Chetrit et al., 2018). Various cleaning and disinfectant techniques have been widely used in health care settings to minimize HAIs. The use of phages as environmental sanitizers has been considered an alternative approach to removing bacterial contamination from the environment. Among the techniques reported, the use of phages as environmental sanitizers successfully decreased the rates of CRAB infection in ICUs (Ho et al., 2016; Chen et al., 2022). Steam technology (Oztoprak et al., 2019), terminal cleaning with sodium tetraclosene (Dickstein et al., 2021), installation of heat and moisture exchangers (Thatrimontrichai et al., 2020), ultraviolet-C, and aerosolized hydrogen peroxide (Kelly et al., 2021) have been successfully applied in environmental disinfection. By contrast, another study reported that strengthened environmental cleaning exhibited no association with the incidence (*p* = 0.156) and colonization pressure (*p* = 0.825) of CRAB in ICUs (Seok et al., 2021). The argument of whether decreasing the use of ventilators is more important than environmental cleaning was presented. A synthesis of the results of these studies indicates that controlling the use of ventilators for environmental disinfection may achieve significantly improved outcomes in infection control.

Figure 3 recapitulates the treatment and infection control of CRAB in ICUs. Collectively, developing an integrated system to monitor the microbial profiles, usage of antibiotics, and resistance profiles in ICUs, as well as combining multiple...
interventions, is necessary for infection control of CRAB in ICUs.

Conclusion

CRAB has progressed as a leading cause of HAIs worldwide, particularly in ICUs. Its spread and multiple-drug resistance considerably impedes the treatment of critically ill patients. On the basis of epidemiology and antibiotic resistance, the combined application of multiple interventions can effectively control the emergence and spread of CRAB, as well as provide hope for the control of CRAB infections in ICUs. Certainly, the implementation of control measures is of crucial importance and has to be extended to other wards for the eradication of CRAB from hospitals.

Author contributions

All authors participated in drafting and revising the review, contributed to the article, and approved the submitted version.

Funding

This study was supported by Sichuan Science and Technology Program (2022YFQ0093 and 2021YFH001).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

Abdallah, M., Badawi, M., Alzaagi, I., Issa, K. N., Rasheed, A., and Alharthy, A. (2019). Effect of short-term carbapenem restriction on the incidence of non-pseudomonal multi-drug resistant gram-negative bacilli in an intensive care unit. J. Chemother. 31, 261–266. doi: 10.1080/1120009x.2019.1601802

Agarwal, S., Kakati, B., Khanduri, S., and Gupta, S. (2017). Emergence of Carbapenem resistant non-fermenting gram-negative bacilli isolate in an ICU of a tertiary care hospital. J. Clin. Diagn. Res. 11, Dc04–Dc07. doi: 10.7860/jcdr/2017/24023.9317

Agodi, A., Auxilia, F., Barchitta, M., Brusaferro, S., D’Errico, M. M., Montagna, M. T., et al. (2015). Antibiotic consumption and resistance: results of the SPIN-UTI project of the GISIO-SItI. Epidemiol. Prev. 39, 94–98.

Al Salman, J., Al Dahal, L., Bassetti, M., Alfouzan, W. A., Al Maslamani, M., Alraddadi, B., et al. (2020). Management of infections caused by WHO critical
predisposition to infections. J. Infect. Public Health. 12, 890–896.

Chen, Y., Li, L., Guo, P., Huang, H., Wu, Z., Luang, X., et al. (2018a). Molecular characterization of multidrug-resistant strains of Acinetobacter baumannii isolated from pediatric intensive care units in a Chinese tertiary hospital. BMC Infect. Dis. 18:614. doi: 10.1186/s12879-018-3511-0

Chen, Y., Li, L., Guo, P., Huang, H., Wu, Z., Luang, X., et al. (2018b). Pseudopatophysiological analysis of cases resistant to multidrug-resistant Acinetobacter baumannii infection: A prospective study. J Electromyogr. Clin. Neurophysiol. 28, 168–174. doi: 10.1016/j.jelecmyo.2018.01.002

Chen, Y. P., Liang, C. C., Chang, R., Kuo, C. M., Hung, C. H., Liao, T. N., et al. (2019). Detection and colonization of multidrug-resistant organisms in a regional teaching Hospital of Taiwan. Int. J. Environ. Res. Public Health 16:1104. doi: 10.3390/ijerph1611104

Chen, Y., Yang, Y., Liu, L., Qu, G., Han, X., Tian, S., et al. (2018b). High prevalence and clonal dissemination of OXA-72-producing Acinetobacter baumannii in a Chinese hospital: a cross-sectional study. BMC Infect. Dis. 18:491. doi: 10.1186/s12879-018-3359-3

Chopulu, B., Tonsk, M. E., Mbelle, N., and Nyafula, P. (2016). Methicillin-resistant Staphylococcus aureus multiresistance surveillance: a systematic review of the literature. Infect. Drug Resist. 9, 35–42. doi: 10.2147/IDR.S95372

Chung, Y. K., Kim, J. S., Lee, S. S., Lee, J. A., Kim, H. S., Shin, K. S., et al. (2015). Effect of daily chlorhexidine bathing on acquisition of carbapenem-resistant Acinetobacter baumannii (CRAB) in the medical intensive care unit with CRAB endemism. Am. J. Infect. Control 43, 1171–1177. doi: 10.1016/j.ajic.2015.07.001

Corve, S., Potrel, L., Naas, T., Drugeon, H., and Nordmann, P. (2007). Genes and expression of the carbapenem-hydrolyzing oxacillinase gene blaOXA in Acinetobacter baumannii. Antimicrob. Agents Chemother. 51, 1530–1533. doi: 10.1128/AAC.01132-06

Dickstein, Y., Elk, O., Warman, S., Abulalba, W., Alon, T., Firaz, I., et al. (2021). Wall painting following terminal cleaning with a chlorine solution as part of an intervention to control an outbreak of carbapenem-resistant Acinetobacter baumannii in a neurosurgical intensive care unit in Israel. J. Infect. Chemother. 27, 1423–1428. doi: 10.1016/j.jiac.2021.05.017

Djordjevic, Z. M., Folic, M. M., Folic, N. D., Gajovic, N., Gajovic, O., and Jankovic, S. M. (2016). Risk factors for hospital infections caused by carbapenem-resistant Acinetobacter baumannii. J. Infect. Dev. Ctries. 10, 1073–1080. doi: 10.3855/jidc.8231

Ehrentraut, S. F., Muenster, S., Kreyer, S., Thuerkauf, N. U., Bode, C., Steinheghen, F., et al. (2020). Extensive therapeutic drug monitoring of Colistin in critically ill patients reveals undetected Microorganisms. 8:415. doi: 10.3390/microorganisms8030415

Ejaz, H., Ahmad, M., Younas, S., Juraid, K., Abosaf, O. A. K., and Abella, A. E. (2021). Molecular epidemiology of extensively-drug-resistant Acinetobacter baumannii sequence type 2 Co-harboring blaOXA and blaOXA from clinical origin. Infect. Drug Resist. 14, 1931–1939. doi: 10.2147/IDR.S10478

Esposito, S., and Leone, S. (2007). Antimicrobial treatment for intensive care unit (ICU) infections including the role of the infectious disease specialists. Int. J. Antimicrob. Agents 29, 494–500. doi: 10.1016/j.ijantimicag.2006.06.017

Garcia-Mercado, C., Gaxiola-Robles, R., Asencio, F., Grajales-Munoz, C., Soriano Rodriguez, M. I., Silva-Sanchez, J., et al. (2021). Antibacterial effect of aetocid acid during an outbreak of carbapenem-resistant Acinetobacter baumannii in an ICU (I). J. Infect. Dev. Ctries. 15, 1167–1172. doi: 10.3855/jidc.1669

Garcia-Mercado, C., Gaxiola-Robles, R., Asencio, F., Silva-Sanchez, J., Estrada Garcia, M. T., and Gomez-Anduero, G. (2020). Development of a LAMP method for detection of carbapenem-resistant Acinetobacter baumannii during a hospital outbreak. J. Infect. Dev. Ctries. 14, 494–501. doi: 10.3855/jidc.11692

Garnacho-Montero, J., Dimopoulos, G., Poulakou, G., Akova, M., Cisneros, J. M., De Waele, J., et al. (2013). Risk factors for management and prevention of Acinetobacter baumannii infections in the ICU. Intensive Care Med. 41, 2057–2075. doi: 10.1007/s00134-015-4079-4

Gorrie, C. L., Mirceta, M., Wick, R. R., Edwards, D. J., Thomson, N. R., Strugnell, R. A., et al. (2017). Gastrointestinal carriage is a major reservoir of multidrug-resistant Acinetobacter baumannii upon intensive care unit admission. Antimicrob. Agents Chemother. 62:17. doi: 10.1128/AAC.01631-17

Guan, X., He, L., Hu, B., Hu, J., Huang, X., Lai, G., et al. (2016). Laboratory diagnosis, clinical management and infection control of the infections caused by extensively drug-resistant gram-negative bacilli: a Chinese consensus statement. Clin. Microbiol. Infect. 22, S15–S25. doi: 10.1016/j.cmi.2015.11.004

Guo, J., and Li, C. (2019). Molecular epidemiology and decreased susceptibility to disinfectants in carbapenem-resistant Acinetobacter baumannii isolated from intensive care unit patients in Central China. J. Public Health. 12, 890–496. doi: 10.1016/j.jiph.2019.08.013

Guth, C., Cavalli, Z., Pernod, C., Lhoptit, C., Wey, P., Gerome, P., et al. (2016). Prompt control of an imported carbapenem-resistant Acinetobacter baumannii outbreak in a French intensive care unit. Medicine et Maladies Tropicales 26, 110–112. doi: 10.14464/mmt15.0517

Haber, N., Paute, J., Gouot, A., Seval Garcia, J., Rouquet, M. L., Sahraoui, L., et al. (2007). Incidence and clinical characteristics of symptomatic urinary infections in a geriatric hospital. Medicine et Maladies Infectieuses 37, 664–672. doi: 10.1016/j.medin.2006.12.004

Harding, C. M., Hennon, S. W., and Feldman, F. M. (2018). Uncovering the mechanisms of Acinetobacter baumannii virulence. Nat. Rev. Microbiol. 16:148. doi: 10.1038/nrmicro.2017.148
He, S., Li, Z., Yang, Q., Quan, M., Zhao, L., and Hong, Z. (2020). Resistance trends among 1, 294 nosocomial Acinetobacter baumannii strains from a tertiary general Hospital in China, 2014–2017. Clin. Lab. 66:629. doi: 10.7754/Clin.Lab.2019.190629

Ho, Y.-H., Tseng, C.-C., Wang, L.-S., Chen, Y.-T., Ho, G.-J., Lin, T.-Y., et al. (2016). Application of bacteriophage-containing aerosol against nosocomial transmission of Carbapenem-resistant Acinetobacter baumannii in an intensive care unit. PloS One 11:e0168380. doi: 10.1371/journal.pone.0168380

Hong, J., Jiang, O. J., Bak, M. H., Baek, E. H., Park, K. H., Hong, S. I., et al. (2018). Management of carbapenem-resistant Acinetobacter baumannii epidemic in an intensive care unit using multifaceted intervention strategy. Korean J. Intern. Med. 33, 1000–1007. doi: 10.3904/kjim.2016.323

Hu, B. (2019). Technical guidelines for prevention and control of carbapenem-resistant gram-negative bacilli infection in China. J. Nosocomiology 29, 2075–2080. doi: 10.1186/s11601-019-191088

Huang, Y.-C., Chou, Y.-H., Su, I.-L., Lien, R.-L., and Lin, T.-Y. (2006). Methicillin-resistant Staphylococcus aureus colonisation and its association with infection among infants hospitalized in neonatal intensive care units. Pediatrics 118, 469–474. doi: 10.1542/peds.2006-0254

Jain, M., Sharma, A., Sen, M. K., Rani, V., Gaind, R., and Suri, J. C. (2019). Pervasive use of aerosolization of Acinetobacter baumannii isolates causing lower respiratory infections among ICU patients. Microb. Pathog. 128, 75–81. doi: 10.1016/j.micpath.2018.12.023

Jiang, M., Mu, Y., Li, N., Zhang, Z., and Han, S. (2018). Carbapenem-resistant from air and patients of intensive care units. PLoS. J. Microbiol. 67, 333–338. doi: 10.2139/psl.infections-2018-08-040

Jung, J., Choe, P. G., Choi, S., Kim, E., Lee, H. Y., Kang, C. K., et al. (2021). Reduction in the acquisition rate of carbapenem-resistant Acinetobacter baumannii (CRAB) after room privatization in an intensive care unit. J. Hosp. Infect. 121, 14–21. doi: 10.1016/j.jhin.2021.12.012

Kalamaris, A. A., Zai, W., and Mirski, M. (2014). Ventilator-associated pneumonia in the ICU. Crit. Care 18:208. doi: 10.1186/cc13775

Kahil, A. C., Metersky, M. L., Klompas, M., Muscedere, J., Sweeney, D. A., Palmer, L. B., et al. (2016). Management of Adults with Hospital-acquired and Ventilator-associated Pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin. Infect. Dis. 63:353. doi: 10.1093/cid/cwz353

Karampatas, T., Tisergoul, K., Josifidis, E., Antachopoulos, C., Mouloudi, E., Karyoti, A., et al. (2020). Forecasting models of infections due to carbapenem-resistant gram-negative bacteria in an intensive care unit in an endemic area. J Glob Antimicrob Resist. 29, 204–218. doi: 10.1016/j.jgar.2019.06.019

Karruli, A., Boccia, F., Gagliardi, M., Patauner, F., Ursi, M. P., Sommese, P., et al. (2021). Multidrug-resistant infections and outcome of critically ill patients with coronavirus disease 2019: a single center experience. Microb. Resist. Disc. 27. 1167–1175. doi: 10.1089/mdr.2020.00489

Karunawati, A., Saharan, Y. R., and Lestari, D. C. (2012). Detection of carbapenemase encoding genes in Enterobacteriaceae, Pseudomonas aeruginosa, and Acinetobacter baumannii isolated from ICU and respiratory department patients of a Chinese university hospital. Infect. Drug Resist. 4, 735–743. doi: 10.2147/tdr.s299540

Ku, Y., Wang, Q., Zhao, C., Chen, H., Li, H., Wang, H., et al. (2020). Prospective multi-center evaluation on risk factors, clinical characteristics and outcomes due to carbapenem resistance in Acinetobacter baumannii complex bacteria: experience from the Chinese antimicrobial resistance surveillance of nosocomial infections (CARES) Network. J. Med. Microbiol. 69, 949–959. doi: 10.1099/jmm.0.001222

Liu, W., Yang, Z., Zhang, K., Bai, H. L., Jiao, Y. P., et al. (2020). Drug resistance of healthcare-associated pathogenic bacteria and carbapenem-resistant Acinetobacter baumannii biomology in the general intensive care unit. Ann Palliat. Med 9, 1545–1555. doi: 10.1007/s10096-017-3098-1

Liu, B., and Liu, L. (2021). Molecular epidemiology and mechanisms of Carbenapen-resistant Acinetobacter baumannii isolates from ICU and respiratory department patients of a Beijing university hospital. Infect. Drug Resist. 14, 743–755. doi: 10.2147/tdr.s299540

Lowe, M., Ehlers, M. M., Isemal, F., Petranio, G., Becker, P. J., Pittout, J. D. D., et al. (2018). Acinetobacter baumannii: epidemiological and Beta-lactamase data from two tertiary academic hospitals in Tshwane, South Africa. Front Microbiol 9:1280. doi: 10.3389/fmicb.2018.01280

Maamar, E., Alono, C. A., Ferjani, S., Jendoubi, A., Hamzaoui, Z., Jebri, A., et al. (2018). NDM-1 and OXA-23 producing Acinetobacter baumannii isolated from intensive care unit patients in Tunisia. Int. J. Antimicrob. Agents 52, 910–915. doi: 10.1016/j.ijantimicag.2018.04.008

Mammina, C., Palma, D. M., Bonora, C., Aleo, A., Fasciana, T., Sodano, C., et al. (2012). Epidemiology and clonality of carbapenem-resistant Acinetobacter baumannii from an intensive care unit in Palermo, Italy. BMC Res Notes 5:365. doi: 10.1186/1756-0500-5-365

Martin, R. M., Cao, J., Brise, S., Passet, V., Wu, W., Zhao, L., et al. (2016). Molecular epidemiology of colonizing and infecting isolates of M. Species 1:e00261. doi: 10.1128/mSphere.00261-16

Mavroidi, A., Katsiari, M., Palla, E., Likou, S., Roussou, Z., Nikolau, C., et al. (2017). Investigation of extensively drug-resistant bla OXA-23 producing Acinetobacter baumannii isolated from a Greek hospital. Microb. Drug Resist. 23, 488–493. doi: 10.1089/mdr.2016.0101

Metan, G., Zarakou, P., Oltu, B., Tekin, I., Aytaç, H., Bökek, E., et al. (2020). Emergence of colistin and carbapenem-resistant Acinetobacter calcoaceticus–Acinetobacter baumannii (CCB-ACH) complex in a neurological intensive care unit followed by successful control of the outbreak. J. Infect. Public Health 13, 564–570. doi: 10.1016/j.jiph.2019.09.013

Mezzatesta, M. L., Caio, C., Gona, F., Cormaci, R., Salerno, I., Zingali, B., et al. (2014). Carbapenem and multidrug resistance in gram-negative bacteria in a single Centre in Italy: considerations on in vitro assay of active drugs. Int. J. Antimicrob. Agents 44, 112–116. doi: 10.1016/j.ijantimicag.2014.04.014
Munta, J. M., and Arias, C. A. (2016). Mechanisms of antibiotic resistance. *Microbiol Spectr* 4:2015. doi: 10.1128/microbiolspec.VMBF-0016-2015

Munoz-Price, L. S., Rosa, R., Castro, J. G., LaNavars, P., Lattebeaudiere, R., Namias, N., et al. (2016). Evaluating the impact of antibiotic exposures as time-dependent variables on the acquisition of Carbapenem-resistant Acinetobacter baumannii. *Crit. Care Med.* 44, e949–e956. doi: 10.1097/CCM.0000000000001848

Nazer, L. H., Kharabsheh, A., Rimawi, D., Mubarak, S., and Hawari, F. (2015a). Characteristics and outcomes of Acinetobacter baumannii infections in critically ill patients with cancer: a matched case-control study. *Microb. Drug Resist.* 21, 556–561. doi: 10.1089/mdr.2015.0032

Nazer, L. H., Rihan, S., Hawari, F. I., and Le, J. (2015b). High-dose colistin for microbiologically documented serious respiratory infections associated with carbapenem-resistant Acinetobacter baumannii in critically ill cancer patients: a retrospective cohort study. * Infect. Dis. (Lond)* 47, 755–760. doi: 10.1097/IMD.0000000000000586

Neves, F. C., Clemente, W. T., Lincopan, N., Paiao, I. D., Neves, P. R., Romanelli, R. M., et al. (2016). Clinical and microbiological characteristics of OXA-23-and OXA-143-producing Acinetobacter baumannii in ICU patients at a teaching hospital. *Brazil. J. Infect Dis* 20, 556–563. doi: 10.1016/j.bjid.2016.08.004

Ng, D. H. L., Marimuthu, K., Lee, J. J., Khong, W. X., Ng, O. T., Zhang, W., et al. (2018). Environmental colonization and onward clonal transmission of carbapenem-resistant Acinetobacter baumannii (CRAB) in a medical intensive care unit: the case for environmental hygiene. *Antimicrob. Resist. Infect. Control* 7:51. doi: 10.1186/s13757-018-0343-2

Nhú, N. T. K., Lan, N. P. H., Campbell, J. L., Parry, C. M., Thompson, C., Buyten, H. H., et al. (2014). Ventilator-associated respiratory infection in a resource-restricted setting: Real-world experience of how chlorhexidine bathing affects the acquisition and concomitant contamination of air and environmental surfaces. *J Glob Antimicrob Resist* 17, 168–172. doi: 10.1016/j.jgar.2018.12.001

Rosa, R., Depascale, D., Cleary, T., Fjardaro-Aquino, Y., Kett, D. H., and Munoz-Price, L. S. (2014). Differential environmental contamination with Acinetobacter baumannii based on the anatomic source of colonization. *Am. J. Infect. Control* 42, 755–757. doi: 10.1016/j.ajic.2014.03.016

Royer, S., Faria, A. L., Seki, I. M., Chagas, T. P., Campos, P. A., Batistão, D. W., et al. (2015). Spread of multidrug-resistant Acinetobacter baumannii and Pseudomonas aeruginosa clones in patients with ventilator associated pneumonia in an adult intensive care unit at a university hospital. *Braz. J. Infect Dis.* 19, 350–357. doi: 10.1016/j.bjid.2015.03.009

Sacco, F., Visca, P., Runci, F., Antonelli, G., and Raponi, G. (2021). Susceptibility testing of Colistin for: how far are we from the truth? *Antibiotics* (Basel, Switzerland) 10:349. doi: 10.3390/antibiotics10040390

Said, K. B., Alsolami, A., Khalifa, A. M., Khalil, N. A., Moursi, S., Osman, A., et al. (2021). A multi-point surveillance for antimicrobial resistance profiles among clinical isolates of gram-negative bacteria recovered from major hospital wards, Saudi Arabia. *Microorganisms* 9:024. doi: 10.3390/microorganisms910024

Salehi, B., Ghavaldan, Z., Mohammadmohassel, M., Maleki, D. T., Kodori, M., and Kadkhoda, H. (2019). Clonal relatedness and resistance characteristics of OXA-24 and OXA-58 producing carbapenem-resistant Acinetobacter baumannii isolates in Tehran. *Iran. J. Appl. Microbiol.* 127, 1421–1429. doi: 10.1111/1440-2197.12839

Salehi, B., Goudarzi, H., Nikmanesh, B., Houri, H., Alavi-Moghaddam, M., and Ghavaldan, Z. (2018). Emergence and characterization of nosocomial multidrug-resistant and extensively drug-resistant Acinetobacter baumannii isolates in Tehran. *Iran. J. Infect. Chemother* 24, 515–523. doi: 10.1016/j.ijic.2018.02.009

Sana, F., Hussain, A., Hussain, W., Zaman, G., Abbas, M. W., Imitar, A., et al. (2021). Frequency and clinical spectrum of multidrug resistant Acinetobacter baumannii as a significant nosocomial pathogen in intensive care unit patients. *J. Ayub Med. Coll. Abbottabad* 33, 752–756.

Schulte, M. B., Pham Thanh, D., Do HoanN, T., Wick, R. R., Ingle, D. J., Hawkey, J., et al. (2016). Repeated local emergence of carbapenem-resistant Acinetobacter baumannii in a single hospital ward. *Microburn Genom* 2, e000050. doi: 10.1099/mgg.0.000530

Seok, H., Jeon, J. H., Jung, J. H., Ahn, S. H., Seo, M., Cho, H. K., et al. (2021). Does enhanced environmental cleaning reduce carbapenem-resistant Acinetobacter baumannii colonization in the intensive care unit? *Int. J. Infect. Dis.* 109, 72–76. doi: 10.1016/j.ijid.2021.06.065

Sharma, A., and Gand, R. (2021). Development of modulated isotheoretical amplification assay for detection of clinically significantly members of Acinetobacter calcoaceticus-baumannii complex and associated Carbapenem resistance. *Front. Mol. Biosci.* 8:659256. doi: 10.3389/fmolb.2021.659256

Shenoy, E. S., Pierce, V. M., Sater, M. R. A., Pangestu, F. K., Herriot, I. C., Anahat, M. N., et al. (2020). Community-acquired in name only: a cluster of carbapenem-resistant Acinetobacter baumannii in a burn intensive care unit and beyond. *Infect. Control Hosp. Epidemiol.* 41, 531–538. doi: 10.1017/ice.2020.15

Shimose, I. A., Masuda, E., Sefîr, M., Berbel Caban, A., Bueno, M. X., de Pascale, D., et al. (2016). Carbapenem-resistant Acinetobacter baumannii: concomitant contamination of air and environmental surfaces. *Infect. Control Hosp. Epidemiol.* 37, 777–781. doi: 10.1017/ice.2016.69

Shirmohammadlou, N., Zeighami, H., Haghif, F., and Keshafei, M. (2018). Resistance pattern and distribution of carbapenemase and antipseudotype resistance genes among multidrug-resistant Acinetobacter baumannii isolated from intensive care unit patients. *Microb. Drug Resist.* 24, 1447–1451. doi: 10.1016/j.mdr.2018.06.008

Suh, J. W., Kim, N. H., Lee, J. M., Lee, S. E., Chun, B. C., Lee, K. C., et al. (2021). Real-world experience of how chlorhexidine bathing affects the acquisition and incidence of vancomycin-resistant enterococci (VRE) in a medical intensive care unit with VRE endemicity: a prospective interrupted time-series study. *Antimicrob. Resist. Infect. Control* 10:160. doi: 10.1186/s13756-021-01030-6

Sunenshine, R. H., Wright, M.-O., Maragakis, L. L., Harris, A. D., Song, X., Hebden, J., et al. (2007). Multidrug-resistant Acinetobacter infection mortality rate...
and length of hospitalization. *Emerg. Infect. Dis.* 13, 97–103. doi: 10.3201/ eid1301.A06716

Taconetelli, E., Carrara, E., Savoldi, A., Harbarth, S., Mendelson, M., Monnet, D. L., et al. (2018). Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect. Dis.* 18, 318–327. doi: 10.1016/S1473-3099(17)30753-3

Tamma, P. D., Atiken, S. L., Bonomo, R. A., Mathers, A. J., van Duin, D., and Clancy, C. J. (2022). Infectious Diseases Society of America guidance on the treatment of ampicillin-lactamase-producing Enterobacteriaceae, Carbapenem-resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia infections. *Clin. Infect. Dis.* 74, 2089–2114. doi: 10.1093/cid/ciab1013

Tanimoto, Y., Tama, S., Matsuzaki, T., Takeuchi, N., Noju, T., Yanagida, S., et al. (2019). Diffusely adherent strains isolated from healthy carriers suppress cytokine secretions of epithelial cells stimulated by inflammatory substances. *Infect. Immun.* 87, e00683–e00618. doi: 10.1128/IAI.00683-18

Thärimontrichai, A., Pannaraj, P. S., Janinathamai, W., Dissanayevate, S., Maneenil, G., and Apsirathanarak, A. (2020). Intervention to reduce carbapenem-resistant in a neonatal intensive care unit. *Infect. Control Hosp. Epidemiol.* 41, 710–715. doi: 10.1017/ice.2020.35

Tiseo, G., Brigante, G., Giacobbe, D. R., Marasol, A. E., Gona, F., Falcone, M., et al. (2022). Diagnosis and management of infections caused by multidrug-resistant bacteria: guideline endorsed by the Italian Society of Infection and Association of Clinical Microbiologists (AMCLI) and the Italian Society of Microbiology (SIM). *Int. J. Antimicrob. Agents* 60:106611. doi: 10.1016/j.ijantimicag.2022.106611

Tomczyk, S., Zanichelli, V., Grayson, M. L., Twyman, A., Abbas, M., Pires, D. et al. (2019). 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.* 68, 873–884. doi: 10.1093/cid/ciy752

Uwingabye, J., Lemnouer, A., Iroca, I., Alouane, T., Frikh, M., Reliquef, B., et al. (2017). Clonal diversity and detection of carbapenem resistance encoding genes among multidrug-resistant isolates recovered from patients and environment in two intensive care units in a Moroccan hospital. *Antimicrob. Resist. Infect. Control* 6:99. doi: 10.1186/s13756-017-0262-4

Venditti, C., Vulcano, A., D’Arezzo, S., Gruber, C. E. M., S Elleri, M., Antonini, M., et al. (2019). Epidemiological investigation of an Acinetobacter baumannii outbreak using core genome multilocus sequence typing. *J. Glob Antimicrob. Resist.* 17, 245–249. doi: 10.1016/j.jgar.2018.11.027

Wang, X., Du, Z., Huang, W., Zhang, X., and Zhou, Y. (2021). Outbreak of multidrug-resistant Acinetobacter baumannii ST208 producing OXA-23-like Carbapenemase in a Children’s Hospital in Shanghai. *China. Microb Drug Resist. 27*, 816–822. doi: 10.1089/mdr.2019.0232

Weisser, J. N., Ferreira, D. M., and Paton, J. C. (2018). Streptococcus pneumoniae: transmission, colonization and invasion. *Nat. Rev. Microbiol.* 16, 355–367. doi: 10.1038/s41579-018-0001-8

Weiss, N., Faugeras, F., Rohaut, B., Leconte, J., Lefaullle, E., Brossier, F., et al. (2016). Multidrug-resistant bacteria transmitted through high-density EEG in ICU. *Seizure* 37, 65–68. doi: 10.1016/j.seizure.2016.03.005

World Health Organization (2011). Report on the burden of endemic health care-associated infection worldwide. World Health Organization. Available at: https://apps.who.int/iris/handle/10665/80135

World Health Organization (2017). Guidelines for the prevention and control of carbapenem-resistant Enterobacteriaceae, Acinetobacter baumannii and Pseudomonas aeruginosa in health care facilities. World Health Organization. Available at: https://apps.who.int/iris/handle/10665/259462

World Health Organization (2022). Global report on infection prevention and control. World Health Organization. Available at: https://apps.who.int/iris/handle/10665/334499

Wu, N., Dai, J., Guo, M., Li, J., Zhou, X., Li, F., et al. (2021). Pre-optimized phage therapy on secondary Acinetobacter baumannii infection in four critical COVID-19 patients. *Emerg Microbes Infect* 10, 612–618. doi: 10.1080/22221751.2021.1902754

Yakupogullari, Y., Othu, B., Ersoy, Y., Kuzucu, C., Bayindir, Y., Kayabas, U., et al. (2016). Is airborne transmission of Acinetobacter baumannii possible: a prospective molecular epidemiologic study in a tertiary care hospital. *Am. J. Infect. Control* 44, 1595–1599. doi: 10.1016/j.ajic.2016.05.022

Yamamoto, N., Hamaguchi, S., Akeda, Y., Santanirand, P., Chaichongsang, N., Sirschot, et al. (2019). Rapid screening and early precautions for carbapenem-resistant Acinetobacter baumannii carriers decreased nosocomial transmission in hospital settings: a quasi-experimental study. *Antimicrob. Resist. Infect. Control* 8:110. doi: 10.1016/j.ajic.2021.06.052

Zhang, Y., Ding, F., Luo, Y., Fan, B., Tao, Z., Li, Y., et al. (2021). Distribution pattern of carbapenemases and solitary contribution to resistance in clinical strains of Acinetobacter baumannii. *Ann Palliat Med* 10, 9184–9191. doi: 10.21037/apm-21-1805

Zhang, X., Li, F., Awan, F., Jiang, H., Zeng, Z., and Lv, W. (2021). Molecular epidemiology and clone transmission of Carbapenem-resistant Acinetobacter baumannii in ICU rooms. *Front. Cell. Infect. Microbiol.* 11:633817. doi: 10.3389/fcimb.2021.633817

Zhang, N., Zhu, L., Ouyang, Q., Yue, S., Huang, Y., Qu, S., et al. (2021). Visualizing the potential impairment of Polymyxin B to central nervous system through MR susceptibility-weighted imaging. *Front. Pharmacol.* 12:784864. doi: 10.3389/fphar.2021.784864

Zhao, Y., Hu, K., Zhang, J., Guo, Y., Fan, X., Wang, Y., et al. (2019). Outbreak of carbapenem-resistant Acinetobacter baumannii carrying the carbapenemase OXA-23-like in ICU of the eastern Heilongjiang Province. *China. BMC Infect Dis.* 19:452. doi: 10.1186/s12879-019-0473-5

Zhen, X., Stålsby Lundborg, C., Sun, X., Gu, S., and Dong, H. (2020). Clinical and economic burden of Carbapenem-resistant infection or colonization caused by Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii: a multicenter study in China. *Antibiotics (Basel)* 9:514. doi: 10.3390/antibiotics9080514

Zhou, Y., Wu, X., Zhang, X., Hu, Y., Yang, X., Yang, Z., et al. (2015). Genetic characterization of ST195 and ST365 Carbapenem-resistant Acinetobacter baumannii harboring blaOXA-23 in Guangzhou. *China. Microb Drug Resist.* 21, 386–390. doi: 10.1089/mdr.2014.0183

Zhou, H., Yao, Y., Zhu, B., Ren, D., Yang, Q., Fu, Y., et al. (2019). Risk factors for acquisition and mortality of multidrug-resistant Acinetobacter baumannii bacteremia: a retrospective study from a Chinese hospital. *Medicine (Baltimore)* 98:e14937. doi: 10.1097/MD.0000000000014937