Outbreak of a carbapenem-resistant XDR *Acinetobacter baumannii* belonging to the International Clone II (IC2) in a clinical setting in Brazil, 2022

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ABSTRACT

Carbapenem-resistant *Acinetobacter baumannii* (CRAB) is a leading cause of nosocomial infections worldwide, and the occurrence of extensively drug-resistant (XDR) lineages among them is increasing. Most of *A. baumannii* pandemic lineages, known as International clones, are represented by MDR/XDR CRAB strains. The IC2 is considered one of the most successful and widespread pandemic clones, however, it is rare in South America, where IC1, IC4 and IC5 are prevalent. In Brazil, besides sporadic reports, an IC2 outbreak was reported only once in São Paulo city during the COVID-19 pandemics. This study characterized an outbreak caused by IC2 strains (n=16) in a hospital in Rio de Janeiro in 2022. MLST (MLST Pasteur scheme) analysis revealed that all strains recovered from nosocomial infections belonged to ST2 and corresponded to CRAB presenting the XDR phenotype. In general, this broad resistance spectrum was explained by the presence of several antibiotic resistance genes (ARGs) (*armA*, bla_{TEM}, $bla_{\text{OXA-23}}$, $bla_{\text{OXA-66}}$, and *aacA4-catB8-aadA1-qacEΔ1/sul1* carried in class 1 integron). Interestingly, the strains characterized here presented a broader resistance spectrum compared to those of the unique other and contemporary IC2 outbreak in Brazil, although they shared most of the ARGs. This study stressed the possibility of the successful establishment of IC2 in Brazilian clinical settings during and after the COVID-19 pandemics in response to a series of events, such as the overuse of antibiotics, during that period.

INTRODUCTION

Acinetobacter baumannii has emerged as one of the most critical opportunistic pathogens for public health worldwide, being frequently involved in ventilator-associated pneumonia, bacteremia, and life-threatening nosocomial infections among severely ill and immunocompromised individuals [1]. This species belongs to the ESKAPE group of pathogens and is featured by its propensity in persisting on inanimate surfaces and acquiring multidrug resistance, which allows it to survive for long periods in the hospital environment. These characteristics contribute to *A. baumannii* person-to-person transmission, and nosocomial spread that favors the successful establishment of infections, leading to a worrisome impact on clinical outcomes [2].

Currently, the golden standard for the treatment of infections caused by *A. baumannii* is carbapenems due to their intrinsic activity against this pathogen [3]. High-risk *A. baumannii* pandemic lineages, named international clones (ICs), generally present a multidrug (MDR) and extensively drug resistance (XDR) character and have been associated with outbreaks around the world. These lineages have mostly been responsible for the spread of carbapenemase genes, such as $bla_{\text{OXA-23}}$, contributing significantly to carbapenem resistance dispersion [4]. So far, several ICs have been more frequently reported, and among them, the IC2 (represented by the ST2 determined by the MLST Pasteur scheme) is the most globally disseminated and prevalent carbapenem-resistant *A. baumannii* (CRAB) lineage that has been involved with difficult-to-treat outbreaks around the world [5-8]. In Brazil, *A. baumannii* of IC1, IC4, IC5 and to a lesser extent, IC7, have been the most prevalent international clones circulating all over the country [9-14]. Moreover, the IC6 international clone ($ST78^{PAS}$/$ST944^{OXF}$) was recently described in the Brazilian Amazon region [15]. However, in spite of the successful IC2 global spread, its occurrence has barely been

reported in Latin America [12,16]. Moreover, IC2 CRAB strains were sporadically described in the Brazilian South region from 1999 to 2002, resurging after ten years (2013-2014). After that, only more recently a local IC2 outbreak was reported in a hospital in São Paulo city [17-21].

Here, we report a recent outbreak caused by CRAB of the IC2 lineage in a hospital in Rio de Janeiro in 2022, and characterize the strains considering their antimicrobial resistance profile, and the presence of genes and elements involved with this phenotype.

METHODS

From June to September 2022, 16 *A. baumannii* strains were recovered from nosocomial infections occurring in a tertiary care hospital placed in Rio de Janeiro. This hospital has 250 beds of which 60 are divided into six ICUs, all of them with medical, surgical and transplantation units. The bacteria were isolated from several clinical specimens (blood, urine, and bronchoalveolar aspirate) of different inpatients placed in the ICUs. Species identification was obtained by VITEK2 Automated System. The *A. baumannii* identification was confirmed by PCR amplification and Sanger sequencing of *cnp60*, and 16S rRNA genes.

The antimicrobial susceptibility test (AST) was determined by the disc-diffusion method for all antibiotics considered for *Acinetobacter spp.* resistance classification [22], and interpreted according to the Clinical and Laboratory Standards Institute (CLSI) [23]. The Disc-diffusion method was also applied for tigecycline, but interpreted to the breakpoints suggested by the FDA for *Enterobacteriaceae* (susceptible ≥19 mm; intermediate 15–18 mm, and resistant ≤14 mm) (https://

www.accessdata.fda.gov/drugsatfda_docs/label/2013/021821s026s031lbl.pdf) [24]. The MIC of polymyxin B and colistin was determined by broth microdilution and interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines (MIC breakpoints for resistance >2mg/L) [25].

The Multilocus Sequence Typing (MLST) based on the Pasteur scheme (PAS) [26] was performed to determine the strains' sequence typing (ST) and to establish their clonal relationship (https://pubmlst.org/organisms/acinetobacter-baumannii). The presence of the most frequent antimicrobial resistance genes involved with resistance emergence to the clinically relevant antibiotics for *Acinetobacter spp.* [22] (bla_{IMP}, bla_{VIM}, bla_{NDM}, bla_{OXA-23}, $bla_{OXA-24-like}$, $bla_{OXA-58-like}$, $bla_{OXA-51-like}$, bla_{GES}, bla_{CTX-M}, bla_{TEM}, *armA*, *rmtD*, *mcr1-5*) were screened by PCR. The presence of IS*Aba1* upstream bla_{OXA} genes was also evaluated. The Quinolone Resistance Determining Region (QRDR) of *gyrA* and *parC* involved with fluoroquinolone resistance emergence in *A. baumannii* was also investigated, as well as the class 1 and 2 integrons and their antibiotic resistance gene content (Table 1).

RESULTS AND DISCUSSION

The MLST analysis revealed that all 16 strains belonged to the international clone IC2. Interestingly, in spite of being a successfully worldwide established clone, the IC2 is sparse and had not been associated with outbreaks in Brazil and South America. After a long period without being detected in Brazil (last reported in 2014) [20], CRAB IC2 resurged in 2020 causing an outbreak in a São Paulo hospital, persisting for at least one year [21]. Interestingly, our study reports the contemporary

occurrence of an IC2 outbreak in another Southeast Brazilian state (Rio de Janeiro), however, presenting a broader resistance profile compared with those IC2 strains of the 2020/2021 outbreak [21].

Our results revealed that, in general, all 16 strains presented the extensively drug resistance (XDR) phenotype, with some slight differences in resistance pattern. They were resistant to all cephalosporins and carbapenems, and susceptible to polymyxins (Table 2). Interestingly, the tigecycline resistance profile was heterogeneous among them (resistant=7; susceptible=9; intermediate=3), suggesting differential regulation of genes involved with this resistance. Therefore, it is worth mentioning that despite the XDR phenotype, these strains were treatable since, besides the polymyxins, some strains were also susceptible to minocycline or tigecycline, which increases the chances of favorable outcomes, mainly if these drugs are used in combination [27].

The PCR analyses revealed that most of the strains carried a class 1 integron harbouring the *aacA4-catB8-aadA1-qacEΔ1/sul1* gene arrangement, which could contribute to aminoglycoside resistance (*aacA4* and *aadA1*). Besides, the search for ARGs revealed the presence of other genes conferring resistance to aminoglycosides (*armA*), β-lactams (bla_{TEM}), and carbapenems ($bla_{\text{OXA-23}}$ and the $bla_{\text{OXA-51}}$ variant, $bla_{\text{OXA-66}}$) in all studied ST2 *A. baumannii* (Table 2). All strains harboured the IS*Aba1* upstream $bla_{\text{OXA-23}}$, which contributed to OXA-23 overexpression. This result demonstrates the important role of *A. baumannii* international clones in OXA-23 and carbapenem resistance dissemination throughout Brazil. Interestingly, IC2 strains incriminated in recent outbreaks among inpatients infected with SARS-CoV-2 in Brazil and Italy [21,28] shared most of the ARGs identified here (*aacA4*, *aadA1*, *catB8*, *armA*, $bla_{\text{OXA-23}}$ and $bla_{\text{OXA-66}}$), indicating that, although transferable, these genes may be well established in the current IC2 lineage circulating worldwide. Moreover, all IC2 strains

harboured the Ser83Leu and Ser80Leu substitutions in the GyrA and ParC, respectively, explaining the observed fluoroquinolone resistance.

Camargo *et al*. [21] suggested that the reemergence and occurrence of an IC2 outbreak in São Paulo could be attributed to several unprecedented factors resulting from COVID-19 pandemics, such as the overuse of antibiotics, the high number of inpatients undergoing invasive procedures, such as mechanical ventilation, and drastic alterations in the hospital routine and infrastructure. This was also the case in the studied hospital, and such factors could also have favored the emergence of the IC2 outbreak and the establishment of this international clone in Rio de Janeiro in the COVID-19 post-pandemic period.

Therefore, the present study reported the current occurrence of the CRAB IC2 presenting the XDR phenotype causing an outbreak in a clinical setting in Rio de Janeiro hospital. The expressive ARG set observed in these strains could impact the overall resistance profile of the bacteria circulating in this hospital, due to the possibility of horizontal transfer of these ARGs.

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AUTHORS'S CONTRIBUTION

Conceptualization, ELF and ACPV; formal analysis, ELF; Collection of data and clinical samples, LAM, PPCO, PMO, LSL, BPS, MARS and AOA; methodology, FSF,

NMSB and SMM; writing – original draft, ELF; writing – review and editing, ELF and ACPV; supervision, ACPV.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

ETHICAL STATEMENT

Ethics committee of FIOCRUZ gave ethical approval for this work under the number 39978114.5.0000.5248.

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282 **Table 1.** Primers used in this study.

Primer name	Primer sequence (5' – 3')
16S RNA F	AGAGTTTGATCCTGGCTCAG
16S RNA R	GTTGCGCTCGTTGCGGGACT
Cnp60 F[a]	ACTGTACTTGCTCAAGC
Cnp60 R[a]	TTCAGCGATGATAAGAAGTGG
IMP F	GAAGGCGTTTATGTTCATAC
IMP R	GTAAGTTTCAAGAGTGATGC
VIM F	GTTTGGTCGCATATCGCAAC
VIM R	AATGCGCAGCACCAGGATAG
NDM F	GGTTTGGCGATCTGGTTTTC
NDM R	CGGAATGGCTCATCACGATC
OXA-51-like F	CGAAGCACACACTACGGGTGTTT
OXA-51-like R	TTCCCTTGAGGCTGAACAAC
OXA-23 F	GATGTGTCATAGTATTCGTCG
OXA-23 R	TCACAACAACTAAAAGCACTG
OXA-58-like F	AAGTATTGGGGCTTGTGCTG
OXA-58-like R	CATCACCAGCTTTCATTTGC
OXA-24 F	ATGAAAAAATTTATACTTCC
OXA-24 R	TTAAATGATTCCAAGATTTTC
ISAba1 F	AGTTGCACTTGGTCGAATGA
ISAba1 R	CATGTAAACCAATGCTCACC
armA F	TGCATCAAATATGGGGGTCT
armA R	GGATTGAAGCCACAACCAAA
rmtD F	GGAAAAGGACGTGGACA
rmtD R	TCCATCGATTCCACAGG
CTX-M F	CGCTTTGCGATGTGCAG
CTX-M R	ACCGCGATATCGTTGGT
TEM F	GTATCCGCTCATGAGACAATA
TEM R	TCTAAAGTATATATGAGTAAACTTGGTCTG
GES F	ATGCGCTTCATTCACGCAC
GES R	CTATTTGTCCGTGCTCAGGA
mcr F	ACCATGCTCCAAAATGCC
mcr R	ATCCATCACGCCTTTTGAGTC
IntI1 F	GGGTCAAGGATCTGGATTTCG
IntI1 R	ACATGCGTGTAAATCATCGTCG
INF	GGCATCCAAGCAGCAAG
INB	GGGCAGACTTGACCTGAT
IntI2 F	GCGTTTTATGTCTAACAGTCC
IntI2 R	AAGTAGCATCAGTCCATCC
GyrA F	AGGACGAACTCAAGCATTCA
GyrA R	GCCAAACAAGCATTCACAAC
ParC F	CGCTCTGTAGCCGAATTTACT
ParC R	CCATCCCAACAGCAATACCT

283 [a] Diancourt *et al.* [26]

284

Table 2. Susceptibility profile and antibiotic resistance genes in the XDR IC2 *A. baumannii* strains of this study

IC2 strains	Antimicrobial resistance profile	ARGs
AB85	AMK, GEN, NET, TOB, IPM, MEM, DOR, CAZ, FEP, CTX, CRO, SAM, TZP, TIM, CIP, LEV, SXT, MIN, TGC	*intI1-aacA4-catB8-aadA1-qacEΔ1/sul1*; *armA;* bla_{TEM}; bla_{OXA-66}; IS*Aba1*-bla_{OXA-23}
AB91	AMK, GEN, NET, TOB, IPM, MEM, DOR, CAZ, FEP, CTX, CRO, SAM, TZP, TIM, CIP, LEV, SXT, TET, DOX, MIN, TGC	*intI1-aacA4-catB8-aadA1-qacEΔ1/sul1*; *armA;* bla_{TEM}; bla_{OXA-66}; IS*Aba1*-bla_{OXA-23}
AB92	AMK, GEN, NET, TOB, IPM, MEM, DOR, CAZ, FEP, CTX, CRO, SAM, TZP, TIM, CIP, LEV, SXT, TET, DOX, MIN, TGC	*intI1-aacA4-catB8-aadA1-qacEΔ1/sul1*; *armA;* bla_{TEM}; bla_{OXA-66}; IS*Aba1*-bla_{OXA-23}
AB93	IPM, MEM, DOR, CAZ, FEP, CTX, CRO, SAM, TZP, TIM, CIP, LEV, SXT, TET, DOX, MIN	*armA;* bla_{TEM}; bla_{OXA-66}; IS*Aba1*-bla_{OXA-23}
AB94	AMK, GEN, NET, TOB, IPM, MEM, DOR, CAZ, FEP, CTX, CRO, SAM, TZP, TIM, CIP, LEV, SXT, TET, DOX, MIN, TGC	*intI1-aacA4-catB8-aadA1-qacEΔ1/sul1*; *armA;* bla_{TEM}; bla_{OXA-66}; IS*Aba1*-bla_{OXA-23}
AB105	AMK, GEN, NET, TOB, IPM, MEM, DOR, CAZ, FEP, CTX, CRO, SAM, TZP, TIM, CIP, LEV, SXT, TET, DOX, MIN	*intI1-aacA4-catB8-aadA1-qacEΔ1/sul1*; *armA;* bla_{TEM}; bla_{OXA-66}; IS*Aba1*-bla_{OXA-23}
AB106	AMK, GEN, NET, TOB, IPM, MEM, DOR, CAZ, FEP, CTX, CRO, SAM, TZP, TIM, CIP, LEV, SXT, TET, DOX, MIN, TGC	*armA;* bla_{TEM}; bla_{OXA-66}; IS*Aba1*-bla_{OXA-23}
AB110	AMK, GEN, NET, TOB, IPM, MEM, DOR, CAZ, FEP, CTX, CRO, SAM, TZP, TIM, CIP, LEV, SXT, TET, DOX, MIN, TGC	*intI1-aacA4-catB8-aadA1-qacEΔ1/sul1*; *armA;* bla_{TEM}; bla_{OXA-66}; IS*Aba1*-bla_{OXA-23}

AB111	AMK, GEN, NET, TOB, IPM, MEM, DOR, CAZ, FEP, CTX, CRO, SAM, TZP, TIM, CIP, LEV, SXT, TET, DOX, TGC	*intI1-aacA4-catB8-aadA1-qacEΔ1/sul1*; *armA;* *bla*$_{TEM}$; *bla*$_{OXA-66}$; IS*Aba1-bla*$_{OXA-23}$
AB112	AMK, GEN, NET, TOB, IPM, MEM, DOR, CAZ, FEP, CTX, CRO, SAM, TZP, TIM, CIP, LEV, SXT, TET, DOX, MIN	*intI1-aacA4-catB8-aadA1-qacEΔ1/sul1*; *armA;* *bla*$_{TEM}$; *bla*$_{OXA-66}$; IS*Aba1-bla*$_{OXA-23}$
AB113	AMK, GEN, NET, TOB, IPM, MEM, DOR, CAZ, FEP, CTX, CRO, SAM, TZP, TIM, CIP, LEV, SXT, TET, DOX, MIN	*armA;* *bla*$_{TEM}$; *bla*$_{OXA-66}$; IS*Aba1-bla*$_{OXA-23}$
AB114	AMK, GEN, NET, TOB, IPM, MEM, DOR, CAZ, FEP, CTX, CRO, SAM, TZP, TIM, CIP, LEV, SXT, TET, DOX, TGC	*intI1-aacA4-catB8-aadA1-qacEΔ1/sul1*; *armA;* *bla*$_{TEM}$; *bla*$_{OXA-66}$; IS*Aba1-bla*$_{OXA-23}$
AB115	AMK, GEN, NET, TOB, IPM, MEM, DOR, CAZ, FEP, CTX, CRO, SAM, TZP, TIM, CIP, LEV, SXT, TET, DOX, TGC	*intI1-aacA4-catB8-aadA1-qacEΔ1/sul1*; *armA;* *bla*$_{TEM}$; *bla*$_{OXA-66}$; IS*Aba1-bla*$_{OXA-23}$
AB116	AMK, GEN, NET, TOB, IPM, MEM, DOR, CAZ, FEP, CTX, CRO, SAM, TZP, TIM, CIP, LEV, SXT, TET, DOX, MIN	*intI1-aacA4-catB8-aadA1-qacEΔ1/sul1*; *armA;* *bla*$_{TEM}$; *bla*$_{OXA-66}$; IS*Aba1-bla*$_{OXA-23}$
AB117	AMK, GEN, NET, TOB, IPM, MEM, DOR, CAZ, FEP, CTX, CRO, SAM, TZP, TIM, CIP, LEV, SXT, TET, DOX, MIN	*intI1-aacA4-catB8-aadA1-qacEΔ1/sul1*; *armA;* *bla*$_{TEM}$; *bla*$_{OXA-66}$; IS*Aba1-bla*$_{OXA-23}$
AB118	AMK, GEN, NET, TOB, IPM, MEM, DOR, CAZ, FEP, CTX, CRO, SAM, TZP, TIM, CIP, LEV, SXT, TET, DOX, MIN, TGC	*intI1-aacA4-catB8-aadA1-qacEΔ1/sul1*; *armA;* *bla*$_{TEM}$; *bla*$_{OXA-66}$; IS*Aba1-bla*$_{OXA-23}$

287 Intermediate resistance are underlined

288

289