Review

Insights on the Horizontal Gene Transfer of Carbapenemase Determinants in the Opportunistic Pathogen Acinetobacter baumannii

Gabriela Jorge Da Silva 1,2, * and Sara Domingues 1,2

1 Faculty of Pharmacy, University of Coimbra, Coimbra 3000-458, Portugal; saradomingues@ff.uc.pt
2 Centre for Neuroscience and Cell Biology, University of Coimbra, Coimbra 3000-458, Portugal
* Correspondence: gjsilva@ci.uc.pt; Tel.: +351-239-488460

Abstract: Horizontal gene transfer (HGT) is a driving force to the evolution of bacteria. The fast emergence of antimicrobial resistance reflects the ability of genetic adaptation of pathogens. Acinetobacter baumannii has emerged in the last few decades as an important opportunistic nosocomial pathogen, in part due to its high capacity of acquiring resistance to diverse antibiotic families, including to the so-called last line drugs such as carbapenems. The rampant selective pressure and genetic exchange of resistance genes hinder the effective treatment of resistant infections. A. baumannii uses all the resistance mechanisms to survive against carbapenems but production of carbapenemases are the major mechanism, which may act in synergy with others. A. baumannii appears to use all the mechanisms of gene dissemination. Beyond conjugation, the mostly reported recent studies point to natural transformation, transduction and outer membrane vesicles-mediated transfer as mechanisms that may play a role in carbapenemase determinants spread. Understanding the genetic mobilization of carbapenemase genes is paramount in preventing their dissemination. Here we review the carbapenemases found in A. baumannii and present an overview of the current knowledge of contributions of the various HGT mechanisms to the molecular epidemiology of carbapenem resistance in this relevant opportunistic pathogen.

Keywords: Acinetobacter; oxacillinases; metallo-β-lactamases; conjugation; transduction; natural transformation; outer-membrane vesicles-mediated transfer; epidemiology; antimicrobial resistance

1. Introduction

Antimicrobial resistance has become a public health problem at a global scale; it limits therapeutic options and thereby increases morbidity, mortality and treatment costs. The emergence of resistance in pathogens and its dynamics in the last decades is the result of an evolutionary process, in part fueled by anthropogenic activities. Resistance can arise by mutation, transmitted vertically through populations by cell division, or through the acquisition of resistance gene(s) from other bacteria belonging to the same generation in a process called horizontal gene transfer (HGT). HGT is recognized as a major evolutionary force that is constantly reshaping genomes. Three principal mechanisms of intercellular transfer are described: natural transformation (transfer of naked DNA to a recipient cell), transduction (phage assisted transfer) and conjugation (direct cell to cell transfer through conjugative plasmids); the latter most often associated with the dissemination of resistance [1]. Additionally, resistance genes can be mobilized by transposable elements within the chromosome and to plasmids (intracellular movement) and vice-versa.

Acinetobacter baumannii emerged as an important opportunistic pathogen with a high ability to acquire antimicrobial resistance and nowadays, many strains are only susceptible to carbapenems and
colistin. However, the finding of carbapenem-resistant strains have been increasing worldwide [2]. As other bacteria, *A. baumannii* contains plasmids and conjugation can undoubtedly explain the dissemination of certain type of carbapenem-resistant genes, such as some OXA-carbapenemases [3,4]. Nevertheless, finding identical integrons with the same resistance genes cassettes arrays in genetically unrelated *A. baumannii* isolates lacking plasmid srules out the paradigm of conjugation as the major driving force in acquisition of exogenous DNA in this species [5]. To gain insights into the intraspecies diversity and the epidemiology of resistance genes it is important to understand the molecular mechanisms underlying the flux of resistance genes among bacteria. Due to the expanded ability of genetic adaptation, the clinical importance and emergent carbapenem resistance of this species, we review the most common carbapenemases produced by *A. baumannii* and the lateral transfer mechanisms of carbapenemase genes involved in their dissemination, in a species that uses all the classic mechanisms referred above and also the more recently identified outer membrane vesicles (OMVs)-mediated transfer.

2. Clinical Importance of *Acinetobacter baumannii*

Members of the genus *Acinetobacter* are considered ubiquitous microorganisms. Its taxonomy has been evolving with the development of molecular and sequencing methods. Species other than *A. baumannii* are found in environmental water and are colonizers of the human skin in some individuals, but not *A. baumannii*, whose habitat remains undefined. Nevertheless, hospital patients may become colonized by this species. It is by far the most clinically important species of *Acinetobacter* as an opportunistic pathogen and it is mostly implicated in infections in critically ill patients hospitalized at Intensive Care Units (ICU). The most frequent hospital-acquired infections by *A. baumannii* are ventilator-associated pneumonia and bloodstream infections, with a considerable morbidity and mortality associated. Other infections include skin and soft tissues infections (such as in burnt patients), wound infections, urinary tract infections and more rarely, secondary meningitis [6]. Therefore, *A. baumannii* has emerged as one of the more problematic opportunistic pathogens in the clinical settings, especially in the last 20 years, now being included in the group of microorganisms which show a high antibiotic resistance index, designated by the acronym ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *A. baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* spp.). Its clinical significance is mostly associated with the ability to quickly acquire antimicrobial resistance to different classes of antibiotics [7]. Additionally, it is one of the Gram-negative bacilli that shows an incredible ability to survive on dry surfaces for prolonged periods, which potentiates its dissemination in the nosocomial environment [8,9].

3. Evolution of Resistance towards Large Spectrum Antibiotics

The absence of large surveillance studies between the 70s and 90s makes the objective analysis of the evolution of resistance of this microorganism and comparison between regions difficult. Moreover, the problem of resistance might be associated with the dissemination of specific clonal lineages. For instance, in Portugal, the first nosocomial isolates of *Acinetobacter* spp. collected in the 1970s–1980s were only resistant to aminopenicillins, first and some second-generation cephalosporins [10]. Also, the identification was not precise and some isolates could not be *A. baumannii*, the prominent species in hospital environments nowadays. After 1999, the scenario changed dramatically with the majority of the isolates showing only susceptibility to tobramycin, amikacin and colistin, which was associated with the European Clone II disseminated all over the country [11–13]. Other European countries reported a similar increase in the isolation of multidrug resistant *A. baumannii* [6,14–16]. It is unquestionable that *A. baumannii*, or at least some lineages [17], have a remarkable ability to acquire resistance determinants and, though its image of a low-virulence pathogen, it cannot be underestimated [18,19]. Often, it is resistant to the majority of classes of antibiotics, including carbapenems, and sometimes colistin, considered the last therapeutic resources for infections caused by multidrug-resistant Gram-negative bacteria [20,21].
4. Carbapenem Resistance in *Acinetobacter baumannii*

Carbapenems (imipenem, meropenem, biapenem, ertapenem, and doripenem) are the β-lactam antibiotics with the broadest spectrum of activity, showing great activity against Gram-negative and Gram-positive bacteria and are considered “last line agents”. Also, they are relatively stable to the majority of β-lactamas, the more frequent reported mechanism of resistance to β-lactam antibiotics. Nevertheless, the resistance to carbapenems has been dramatically increasing over recent years among the Gram-negatives [22,23].

Diverse other mechanisms may be responsible for carbapenem resistance in *A. baumannii*. The loss or alterations of specific outer-membrane proteins have been reported to play a role in carbapenem resistance (CarO) [24]. Occasional reports associated the resistance to carbapenems to modification of penicillin binding proteins (PBPs) [25]. The AdeABC efflux pump, belonging to the resistance nodulation division family of efflux systems (RND) and associated with the efflux of antibiotics with diverse structures [26], was shown to be present in *A. baumannii* [27,28] and eventually to play some role in carbapenem resistance. However, the latter resistance mechanism appeared to give clinical resistance to carbapenems only when associated with others, namely the production of carbapenem-hydrolysing oxacillinas [29,30].

5. Production of Carbapenemases

5.1. Intrinsic β-Lactamas

*A. baumannii* produces intrinsic β-lactamas such as an AmpC-type cephalosporinase expressed at low levels. However, when the insertion sequence IS*Aba1* is located upstream the *bla*AmpC gene, its expression is enhanced and provides resistance to 3rd generation cephalosporins, but not to carbapenems.

Additionally, it seems that the majority of *A. baumannii* strains produce oxacillinas represented by OXA-51/69 variants [31,32]. These enzymes show weak hydrolytic activity towards carbapenems. However, isolates bearing the IS*Aba1*-bla*OXA-51*-like gene, show higher rates of resistance to imipenem and meropenem [33,34]. The *bla*OXA-51*-type are usually located in the chromosome. It has been suggested its use as a marker for identification of the species [35] but it has also been shown that other species may eventually carry this oxacillinase in plasmids [36,37]. Detection of target site duplications surrounding transposon Tn*6080*, which carry the *bla*OXA-51*-like gene in *A. baumannii* plasmids, suggest that this genetic element has moved by transposition from the chromosome of this species [34]. Transfer of plasmid-carrying *bla*OXA-51*-like by HGT, probably conjugation, to non-*baumannii* species has probably occurred. Conjugation of plasmids carrying the *bla*OXA-51*-like gene from *Acinetobacter nosocomialis* to *A. baumannii* was observed [37].

5.2. Acquired β-Lactamas

The most striking activity against to carbapenems in *A. baumannii* has been described by the acquisition of diverse carbapenemase encoding-genes. Carbapenemases are a group of enzymes that are able to hydrolyse carbapenems even at low level. The emergence of infections caused by extended spectrum β-lactamas (ESBLs) Gram-negative producers in the early 1990s, concomitantly resistant to other classes of antibiotics such as quinolones and aminoglycosides, lead to the more frequent use of carbapenems in complicated infections, which may be associated with the emergence and spread of carbapenemases through all continents [38–40].

Carbapenemases belong to three classes of the Ambler classification [41]: the class B, comprising the metallo-β-lactamas (MBLs) that require a bivalent metal ion, usually Zn$^{2+}$, for activity; and the class D, the typical class of oxacillinas, and to class A. The former are potent carbapenemases with the ability to hydrolyse all β-lactams, except aztreonam. To date, three families of MBLs have been identified in *A. baumannii*: the IMP-, the VIM- and NDM-types. Although the *bla*SIM-1 gene was described for the first time as part of the class 1 integron present in seven clinical isolates of
A. baumannii in 2005 [42], the isolates were later identified as A. pittii [43]. So far, there are no reports on the presence of this gene in A. baumannii. Oxacillinases are a heterogeneous group of β-lactamases with higher efficiency in the hydrolysis of oxacillin than benzylpenicillin [44]. Only a sub-group of oxacillinases have the ability of inactivating carbapenems, usually not as efficiently as MBLs and are named carbapenem-hydrolysing class D β-lactamases (CHDLs). The acquired sub-group of CHDLs in A. baumannii can be clustered in: OXA-23-like, OXA-40/24-like; OXA-58-like [3]; OXA-143-like [45]; and OXA-235-like [46] (Table 1). To our knowledge, only one study reports the finding of the blaOXA-48 gene in A. baumannii. However, identification of the location and genetic environment of the gene was not the focus of this report [47].

Both MBLs and CHDLs are resistant to the β-lactam inhibitors clavulanic acid and tazobactam [44].

6. Mechanisms of Acquisition of Carbapenemase Determinants in Acinetobacter baumannii

Despite the numerous reports on the mechanisms of the acquisition of exogenous DNA by bacteria, our knowledge is far from complete in explaining the rapid genetic evolution of bacteria. Some species seem more prone to acquiring exogenous DNA than others. A. baumannii has undoubtedly an enormous genetic plasticity in order to survive.

Members of the Acinetobacter genus can exploit four different HGT mechanisms to exchange genetic material. Conjugation is reported to have the greatest impact in the dissemination of antimicrobial resistance [48]. Transduction and transformation are apparently less important, yet recent studies suggest that their role may be more expressive than initially thought.

All of the HGT mechanisms have been specifically observed in A. baumannii. Many of the blaOXA genes and some MBLs determinants, such as blaNDM genes, are found to be plasmidic, suggesting that conjugation has an important role in the dissemination of these carbapenemases determinants. Nonetheless, a few studies failed to demonstrate conjugation of plasmids in this species [49–52] and quite often their dissemination is inferred from their plasmid location, especially in epidemiological studies where conjugation assays are not demonstrated. Moreover, the isolation and study of Acinetobacter plasmids has been shown to be a difficult task, which may be a limiting factor in experimental assays [52,53]. A few studies have experimentally shown transduction in A. baumannii [54,55]. Natural transformation is known to occur in the Acinetobacter genus [56]. However, this mechanism has not been demonstrated to occur in clinical A. baumannii isolates until recently. Indeed, two studies and our own current research identified naturally competent strains of A. baumannii; this species can under certain conditions take up both chromosomal and plasmid DNA [57,58], leading to the hypothesis that natural transformation may have some influence in the dynamics of resistance genes in A. baumannii. Another mechanism was also demonstrated in A. baumannii, where plasmid DNA transfer can be mediated by OMVs [59], a mechanism not frequently reported in explaining the dissemination of resistance genes and most probably underestimated.

The next chapters will review the mechanisms of the horizontal transfer of carbapenemase genes in A. baumannii. Unlike the majority of oxacillinases in other genera, none of the A. baumannii blaOXA genes associated with carbapenem resistance have been found in integrons [2,60]. On the other hand, some MBLs are embedded as gene cassettes in integrons, which are not self-mobile but are often inserted into mobile elements [2,61].
### Table 1. Carbapenemase Genes in *Acinetobacter baumannii*: Genetic Location, Horizontal Gene Transfer Mechanisms, Genetic Context and Movement of Mobile Genetic.

| Carbapenemases | *bla* Gene Type | Resistance Origin | Location | Intercellular Transfer (HGT) | Genetic Context | Intracellular Movement | References |
|----------------|-----------------|-------------------|----------|-----------------------------|-----------------|------------------------|------------|
| CHDLs 2        | OXA-51          | Intrinsic         | Mainly chromosomal; plasmid | Tn6080               | Sometimes, ISAba1-blaOXA-51-like | Transposition      | [33,35] |
| OXA-23         | Acquired        | Chromosome and plasmid | Conjugation | Genomic islands; Transposons; Insertion sequences | Transposition | [62–73] |
| OXA-40/24      | Acquired        | Chromosome and plasmid | Conjugation? 5 | Self-transmissible plasmid belonging to replicon group GR6 and in plasmids containing mob genes | Transposition | [45,74–77] |
| OXA-58         | Acquired        | Mostly plasmidic | Conjugation? 5 | Self-conjugative plasmid belonging to replicon group GR6 | Insertion sequences | Flanked by two repeated sequences, Re27 | Homologous recombination | [32,67,81–83] |
| OXA-143        | Acquired        | Plasmid           | Flanked by two rep genes | Homologous recombination | Flanked by two IS26 leading to duplication of ISAba2/ISAba3-blaOXA-58-ISAba3 | Transposition | [84] |
| OXA-235        | Acquired        | Chromosome and plasmid | Flanked by two ISAba1 | XerC/XerD recognition site | Site-specific recombination | Flanked by two IS26 leading to duplication of ISAba2/ISAba3-blaOXA-58-ISAba3 | Transposition | [45] |

OMVs 4-mediated transfer

[59]
Table 1. Cont.

| Carbapenemases | bla Gene Type | Resistance Origin | Location | Intercellular Transfer (HGT) | Genetic Context | Intracellular Movement | References |
|----------------|---------------|-------------------|----------|-----------------------------|----------------|------------------------|------------|
| MBLs \(^3\)   | IMP           | Acquired          | Chromosome and plasmid | Conjugation | Many inserted in class 1 integrons | [88–93]             |
|                |               |                   |          |                             | Gene not embedded into integrons | [94]             |
|                |               |                   |          | Natural transformation     | Class 1 integron flanked by MITEs \(^6\) | [95,96] |
|                |               |                   |          |                             | Homologous recombination | [89,97] |
| VIM            | Acquired      | Chromosome        | Class 1 and 2 integrons | Conjugation | Associated to composite transposon Tn125 | [98–102], GenBank Ac. nr. LC107606 |
| NDM            | Acquired      | Mostly plasmidic; | Conjugation | Associated to composite transposon Tn125 | Transposition | [103–110] |
|                |               | chromosome        |          |                             | Flanked by ISAlba125 and ISCR21 | [111] |
| Class A \(\beta\)-lactamases | KPC       | Acquired          | Chromosome | Tn4401b embedded into KQ-like element | Transposition | [112] |
|                |               |                   |          |                             | (Novel truncated version of) Tn4401e | [113] |
| GES            | Acquired      | Chromosome and plasmid | Conjugation | Class 1 integrons | [114–119] |

\(^1\) HGT, Horizontal gene transfer; \(^2\) CHDLs, Carbapenem-hydrolysing oxacillinases; \(^3\) MBLs, Metallo-\(\beta\)-lactamases; \(^4\) OMVs, Outer-membrane vesicles; \(^5\) Failed demonstration [50,51,76,78,120]; \(^6\) MITEs, Miniature inverted repeat transposable elements.
6.1. Mechanisms Involved in the Movement and Dissemination of CHDLs

6.1.1. OXA-23 (and OXA-23-Like)

The \( \text{bla}_{\text{OXA-23}} \) (previously known as \( \text{bla}_{\text{ARI-1}} \)) gene, identified for the first time in a clinical \( A. \text{baumannii} \) isolate collected in 1985 [62,63], can be inserted both in the chromosome and in plasmids and be surrounded by different genetic contexts, such as genomic islands (AbaR4, AbaR25 and AbaR26), transposons (Tn2006, Tn2007, Tn2008, Tn2009 and Tn6206) and insertion sequences (ISs) [64–67].

The \( \text{bla}_{\text{OXA-23}} \) gene, which is nowadays widely distributed in \( A. \text{baumannii} \), was originally naturally present in \( A. \text{radioreisens} \) strains, though not expressed and a sequence of different transposition and horizontal transfer events have probably resulted in the transfer of this gene to \( A. \text{baumannii} \) [66,121]. This gene has been identified in other \( A. \text{baylyi} \) strains, namely \( A. \text{baylyi} \) [122], \( A. \text{johnsonii} \) [123], \( A. \text{gandensis} \) [124], \( A. \text{genomic species 14TU/13B} \) [125], \( A. \text{nosocomialis} \) [125] and \( A. \text{pittii} \) [123]. The same genetic context of the \( \text{bla}_{\text{OXA-23}} \) gene in \( A. \text{baumannii} \) is found in some of these species, suggesting occurrence of HGT [53,67,122,125,126]. There are also three reports on the detection of the \( \text{bla}_{\text{OXA-23}} \) gene in two species of the \( \text{Enterobacteriaceae} \) family, namely \( \text{E. coli} \) [127] and \( \text{P. mirabilis} \) [128,129]. While the \( \text{bla}_{\text{OXA-23}} \) gene in \( P. \text{mirabilis} \) is chromosomally-located [128,129], the gene found in \( E. \text{coli} \) is flanked by two IS1 elements and it is located on a non-self-conjugative plasmid, which failed conjugation to \( E. \text{coli} \) and \( A. \text{baumannii} \) recipient strains [127].

Expression of this gene in \( A. \text{baumannii} \) is associated with the presence of ISAb1 insertion sequences, especially ISAb1, preceding it [33,66,68,69]; the association of ISAb1 with \( \text{bla}_{\text{OXA-23}} \) has also been implicated in the movement of this gene by transposition, as experimentally shown [70] or as reflected by the identification of target site duplications surrounding the composite-transposons [66,67,69].

Horizontal transfer of this gene due to plasmid conjugation between \( A. \text{baumannii} \) strains has been demonstrated [64,71,72]; conjugation of a plasmid-carrying \( \text{bla}_{\text{OXA-23}} \) from \( A. \text{baumannii} \) to \( A. \text{baylyi} \) [130] has also been shown. Intracellular movement of transposons-carrying the \( \text{bla}_{\text{OXA-23}} \) gene by transposition can be suggested due to the identification of target site duplications surrounding the transposons, as determined by nucleotide sequencing of the genetic context of the gene in wildtype \( A. \text{baumannii} \) strains [64,71,73]; the same is valid for genomic islands [72].

Evidence of HGT has also been inferred from the different chromosomal insertion sites of the \( \text{bla}_{\text{OXA-23}} \) gene in isolates belonging to the same clonal complex [130]. Other evidence demonstrating the horizontal movement of the \( \text{bla}_{\text{OXA-23}} \) gene associated with the ISAb1 mobile element has come from the fact that the same genetic context is detected in several genetically unrelated isolates [68].

6.1.2. OXA-40/24 (and OXA-40-Like)

The \( \text{bla}_{\text{OXA-40}} \) (firstly identified as \( \text{bla}_{\text{OXA-24}} \)) gene was identified for the first time in a clinical \( A. \text{baumannii} \) strain isolated in 1997 [74,131]. The \( \text{bla}_{\text{OXA-40}} \) and \( \text{bla}_{\text{OXA-40-like}} \) genes reported in \( A. \text{baumannii} \) are located both in the chromosome [74–76] and in plasmids [45,76,77]. However, experimental demonstration of conjugation of \( A. \text{baumannii} \) plasmid-encoding \( \text{bla}_{\text{OXA-40-like}} \) genes into \( A. \text{baumannii} \) and \( E. \text{coli} \) have failed [76,78]. Nonetheless, the presence of this gene in plasmids belonging to the replicon group GR6, which are self-transmissible and in plasmids containing \( \text{mob} \) genes, which can be mobilized by self-transmissible plasmids, indicates a potential for horizontal dissemination by conjugation [52,78]. The lower GC content of the \( \text{bla}_{\text{OXA-40}} \) gene, as compared with the remaining genome of \( A. \text{baumannii} \), suggests a different species as the source of this gene [3].

The \( \text{bla}_{\text{OXA-40}} \) gene found in the \( A. \text{baumannii} \) chromosome or in different plasmids is not embedded into the typical structures involved in DNA mobilization such as ISs but is instead flanked by conserved inverted repeats homologous to XerC/XerD binding sites [77,79,80]. These sites are the targets of the XerC and XerD recombinases, which are involved in site-specific recombination mechanisms. It is suggested that the \( \text{bla}_{\text{OXA-40}} \) gene can be mobilized by this mechanism within...
the *A. baumannii* isolates and then further spread by HGT. This hypothesis is supported by the fact that the same structure is located in different plasmids and in the chromosome [77,78] and that the same binding sites flank different DNA modules in other locations [79]. Identification of genes involved in the toxin/antitoxin system in plasmids harboring the *bla*$_{OXA-40}$ gene might explain the wide dissemination and stability of the plasmids containing this gene [132].

This gene has been occasionally reported in other *Acinetobacter* species such as *A. baylyi* [133], *Acinetobacter calcoaceticus* [77], *Acinetobacter haemolyticus* [134] and *A. pittii* [125]. The same plasmid containing the *bla*$_{OXA-40}$ gene flanked by the XerC/XerD binding sites has been found in *A. baumannii*, *A. calcoaceticus* [77], *A. baumannii* and *A. haemolyticus* [78], which suggests transfer of this genetic element from *A. baumannii* to the other species, by a HGT mechanism that has not yet been determined. The *A. baumannii* *bla*$_{OXA-40}$ gene has also been detected in *P. aeruginosa*, in a plasmid similar to one found in *A. baumannii* [135].

OMVs of Gram-negative bacteria serve a wide number of biological functions and have been extensively studied in the delivery of proteins and toxins in order to target cells during infection, and therefore, are mostly associated with virulence factors [136]. Nevertheless, Rumbo and colleagues [59] have experimentally shown the release of OMVs containing the plasmid-encoded *bla*$_{OXA-24}$ from carbapenem-resistant *A. baumannii* clinical strains that were able to transform a carbapenem-susceptible *A. baumannii* strain. The transformants maintained the capacity to release OMVs containing the plasmid-encoded *bla*$_{OXA-24}$. The OMVs-mediated transfer remains largely unexplored in the spread of antimicrobial resistance and this study has been the first experimental evidence that clinical isolates of *A. baumannii* may release OMVs carrying carbapenemase determinants as a mechanism of HGT.

6.1.3. OXA-58 (and OXA-58-Like)

The *bla*$_{OXA-58}$ gene was identified for the first time in 2003 in a clinical *A. baumannii* isolate [120]. This gene is usually plasmid-encoded and it is found in different plasmids [67,81,82]. Despite the plasmid location, several attempts have failed to demonstrate conjugation of this genetic mobile element between *A. baumannii* or from *Acinetobacter* spp. to *A. baumannii* strains [50,51,120]. Therefore, the involvement of natural transformation, transduction and/or OMVs-mediated transfer could eventually explain the wide spread of the plasmid-encoded *bla*$_{OXA-58}$ gene.

The existence of similar plasmid-carrying *bla*$_{OXA-58}$ in unrelated strains and with different origins (clinical vs. hospital environment) is seen has evidence of the HGT of this element [51]. Although sporadically, this gene has also been detected in other *Acinetobacter* species, including *Acinetobacter bereziniae* [137], *Acinetobacter guillouiae* [138], *A. johnsonii* [139], *Acinetobacter junii* [81], *Acinetobacter lwoffi* [137], *A. nosocomialis* [50], *Acinetobacter phenon 6/c13TU* [140], *A. pittii* [50,141], *A. radioresistens* [142] and *Acinetobacter seifertii* [143]. One recent study has observed a possible mobilization of a plasmid-encoding *bla*$_{OXA-58}$ during conjugation of a self-transmissible plasmid from *A. pittii* to *A. baumannii* [144]. It has been suggested that in *A. baumannii* plasmid-encoding, *bla*$_{OXA-58}$ can be mobilized by the self-conjugative plasmids belonging to the replicon group G6 [52,83].

In *A. baumannii* the *bla*$_{OXA-58}$ gene is surrounded by IS*Aba3* [3] however the upstream IS*Aba3*-like element is often disrupted by different ISs such as IS*Aba1*, IS*Aba2* [84], ISO*Our1*, IS1008, IS15 [50] and IS*Aba25* [85], which enhance the expression of the *bla*$_{OXA-58}$ gene. Despite the fact that the *bla*$_{OXA-58}$ gene is surrounded by these mobile elements and that similar *bla*$_{OXA-58}$ genetic contexts are found in different *Acinetobacter* species and strains [50,84,141], there is little evidence that this structure has moved by transposition [3]. Rather, it is proposed that the acquisition of the *bla*$_{OXA-58}$ gene and respective genetic context resulted from homologous recombination events, evidenced by the fact that different genetic structures containing the gene are flanked by two repeated sequences called Re27 [84]. The same recombination sites and the *bla*$_{OXA-58}$ gene and respective gene surrounding has been identified in *A. nosocomialis* and *A. pittii* [50]. There is only one study that suggests that the *bla*$_{OXA-58}$ gene flanked by an IS*Aba3* and an intact IS*Aba3*-like elements as transposed into a plasmid in *A. pittii* [144]. The duplication of an IS*Aba2*/IS*Aba3*-*bla*$_{OXA-58}$-IS*Aba3* unit in clinical *A. baumannii*
isolates has been linked to the action of two IS26 elements surrounding the previous unit; multiple copy numbers of the \( \text{bla}_{\text{OXA-58}} \) gene was correlated with increased Minimum Inhibitory Concentrations of carbapenems [86].

It has been suggested that the \( \text{bla}_{\text{OXA-58}} \) gene widely disseminated among \( A. \text{baumannii} \) strains has its source in a different species, reflected by the different GC content of the gene, when compared with its core genome [3]. However, the source has not been identified so far.

Recently, the mechanism of dissemination of OXA-58 CHDL was elucidated. Not being exactly a mechanism of gene transfer, the formation of OMVs by \( A. \text{baumannii} \) also contributed to the release of extracellular OXA-58 CHDL. OXA-58 is selectively released via OMVs after using the Sec-dependent periplasmic translocation transport system and its release was increased upon a carbapenem challenge [145]. These OMVs have a sheltering effect on carbapenem-susceptible bacteria allowing the unexpected survival of the cells in, for example, polymicrobial infections [145,146]. Yet not sharing genetic material, the overexpression of OXA-58 by \( A. \text{baumannii} \) protects other bacteria. However, as in the case of the transfer of \( \text{bla}_{\text{OXA-40}} \) OMVs, the genetic exchange cannot be discarded.

6.1.4. OXA-143 (and OXA-143-Like)

The OXA-143 sub-group of CHDLs was described for the first time in \( A. \text{baumannii} \) in 2009; the \( \text{bla}_{\text{OXA-143}} \) gene was plasmid located and flanked by two copies of the same replicase gene, suggesting acquisition by homologous recombination [45].

One \( \text{bla}_{\text{OXA-143}} \)-like gene, \( \text{bla}_{\text{OXA-253}} \), was also detected as part of a plasmid that resembles one plasmid carrying the \( \text{bla}_{\text{OXA-40/24}} \) gene; acquisition of the \( \text{bla}_{\text{OXA-253}} \) gene is suggested to have occurred by site-specific recombination in the XerC/XerD site [87].

All isolates reported to carry a \( \text{bla}_{\text{OXA-143}} \)-like gene so far were isolated in Brazil [45,87,147–149]. None of the published studies have performed HGT assays that could be involved in the dissemination of these CHDLs. However, horizontal transfer might be inferred from the presence of the same gene in diverse genotypes [147].

6.1.5. OXA-235 (and OXA-235-Like)

Recently, a new subclass of CHDL was identified, the OXA-235. The \( \text{bla}_{\text{OXA-235}} \) gene has been found both in the chromosome and in plasmids. These genes have been found flanked by two IS\( \text{Aba1} \), suggesting that they can potentially move by transposition [46].

6.2. Mechanisms Involved in the Movement and Dissemination of MBL Genes

Some MBLs are inserted in integrons that may be integrated in mobile genetic elements such as transposons; some are chromosomal, others are located in plasmids, which may more easily explain their dissemination. Integrons are genetic elements that can capture gene cassettes by site-specific recombination. Any gene cassette embedded in an integron that enters a cell by HGT mechanisms can potentially be recruited by an already existing integron [150] but this has not been experimentally demonstrated with MBL-encoding genes. The MBL-encoding genes present in \( A. \text{baumannii} \) can be found in a variety of different cassette arrays (http://integrall.bio.ua.pt/).

6.2.1. IMP-Type

From the 52\( \text{bla}_{\text{IMP}} \) gene variants that have been described [151], at least 12 have been detected in \( A. \text{baumannii} \) [2,88] (GenBank accession number KT935306).

The \( A. \text{baumannii} \) class 1 integrons carrying \( \text{bla}_{\text{IMP}} \) genes can be chromosomally- [89–91] or plasmid-located [88,92,93]. Class 1 integrons carrying \( \text{bla}_{\text{IMP}} \) genes are also often found in Enterobacteriaceae, usually in transferable plasmids [61,152], which does not seem to be the case in \( A. \text{baumannii} \) [92,152]. Conjugation of plasmids-carrying the \( \text{bla}_{\text{IMP-5}} \) gene from \( A. \text{bereziniae} \) to \( A. \text{baumannii} \) has also been unsuccessful [153]. Conjugation of a \( \text{bla}_{\text{IMP}} \) gene between \( A. \text{baumannii} \) strains has been reported by Takahashi and colleagues [154]. However, the authors did not detect
plasmids in their donor isolates, often difficult to isolate in this species, but it opens up the possibility of the transfer of the bla\textsuperscript{IMP} gene by another HGT mechanism. Nonetheless, bla\textsuperscript{IMP} genes are not always embedded in integrons and conjugation of a plasmid-carrying the bla\textsuperscript{IMP-1} gene not associated with class 1 integron from \textit{A. baumannii} to \textit{E. coli} was reported [94].

The presence of the same class 1 integron in different bacterial species and genus is seen as an evidence of HGT [91,150,152].

Evidence of the intracellular movement by transposition of a class 1 integron-carrying the bla\textsuperscript{IMP-5} gene flanked by miniature inverted repeat transposable elements (MITEs) in \textit{A. baumannii} can be inferred from the determination of target site duplications on both sides of the MITEs [95]; identical MITEs were found flanking the integron-carrying bla\textsuperscript{IMP-1} gene in \textit{A. baumannii} isolates [96].

Intercellular transfer of chromosomally-located genes cannot be explained by conjugation. So far, there are no reports on the dissemination of carbapenem-resistance genes by natural transformation between \textit{A. baumannii} strains, which could be explained by the fact that only very recently has this species been shown to be competent in specific conditions [57,58]. Nonetheless, the hypothesis that \textit{A. baumannii} could be a source for carbapenem-resistance genes dissemination due to natural transformation events cannot be neglected. It was experimentally demonstrated that the chromosomal class 1 integron-carrying bla\textsuperscript{IMP-5} of the clinical \textit{A. baumannii} 65FFC strain [89] was transferred by natural transformation to the integron-carrying \textit{A. baylyi} SD2 (derivative of strain BD413) and incorporated into the recipient’s chromosome by homologous recombination of the conserved regions of this class of integron [97]. From this study we might infer that carbapenem-resistance genes incorporated into class 1 integrons can be potentially acquired by all natural competent species that do not restrict the DNA uptake to the species level.

6.2.2. VIM-Type

Forty-eight bla\textsuperscript{VIM} gene variants have been described so far [151]; among these, only six have been reported in \textit{A. baumannii} [2]. The bla\textsuperscript{VIM} genes embedded into class 1 integrons have been identified in a limited variety of gene cassette arrays in \textit{A. baumannii} and are not frequently reported in this species; reports on these genes are more abundant and diverse in \textit{P. aeruginosa} [155,156]. The bla\textsuperscript{VIM-2} gene has also been identified in a class 2 integron in \textit{A. baumannii} (GenBank accession number LC107606).

Most of the studies do not report on the genetic environment of the class 1 integrons carrying the bla\textsuperscript{VIM} genes [98–100], which hinders the unravelling of the horizontal mechanisms involved in their dissemination; these have been described in the chromosome of \textit{A. baumannii} but without further analysis of the genetic context [101,102]. Up to now, there have been no studies showing the horizontal transfer of VIM determinants in \textit{A. baumannii}. Horizontal transfer of VIM-encoding genes can be inferred from the presence of the same integron in genetically non-related \textit{A. baumannii} isolates [98,157], in different species and genus [158]. Conjugation of bla\textsuperscript{VIM-1} genes from \textit{A. baumannii} to \textit{E. coli} has failed. However, it is not clarified if this failure is due to chromosomal location of the gene or due to inability of the plasmid to conjugate [98].

6.2.3. NDM-Type

Since the identification of the New Delhi metallo-\(\beta\)-lactamase (NDM) in 2008 in India, this MBL has been reported worldwide. The bla\textsuperscript{NDM} genes have been recognized in a variety of species and genus and its location in diverse replicon type plasmids, such as IncA/C2 and IncFIIX plasmids, is the most likely mechanism in explaining this expanded dissemination [103]. Some examples are further mentioned.

Until now, 16 variants of the bla\textsuperscript{NDM} gene have been identified [151]. Three of these variants, namely bla\textsuperscript{NDM-1}, bla\textsuperscript{NDM-2} and bla\textsuperscript{NDM-3} were identified in \textit{A. baumannii} [159,160] (GenBank accession number KU220611).

Interestingly, a clinical case in China reports the finding of bla\textsuperscript{NDM-1} in \textit{E. coli}, \textit{Citrobacter freundii} and \textit{A. baumannii} collected from the same patient but while bla\textsuperscript{NDM-1} was inserted in an identical
plasmid in the Enterobacteria, in *A. baumannii* it was found to be located in a very large plasmid (>400-Kb) [104]. The genetic environment was not analysed. The *blaNDM-1* determinant was also located in a plasmid of 100-Kb in an isolate from Brazil [105]. In Switzerland, the *blaNDM-1* gene has been found in Enterobacteria located on conjugative IncA/C- or IncF-type plasmids. In all strains, part of IS*Aba125*, previously identified in *blaNDM-1*-negative *A. baumannii*, was found upstream of the *blaNDM-1* gene, suggesting that the original dissemination occurred from *A. baumannii* [106]. This carbapenemase can also be found in animals. An isolate of *A. baumannii* positive for *blaNDM-1* was collected from a lung sample of a pig with pneumonia and sepsis. The *blaNDM-1* gene was located in a ~47-Kb plasmid. This plasmid could be transferred by conjugation at the high frequency of $1.15 \times 10^{-2}$ per donor cell into *E. coli* J53 [107]. Therefore, it seems that in the case of *blaNDM*-type, conjugation plays an important role in the spread of carbapenem resistance and diverse conjugative plasmids are involved.

Nonetheless, the *blaNDM-1* can also be chromosomally located. In fact, *blaNDM-1* seems to be usually flanked by two IS*Aba125* insertion sequences, a structure corresponding to the composite transposon Tn125 [108,109,159]. This transposon was also associated with *blaNDM-2*, suggesting that Tn125 is the major vehicle for the dissemination of *blaNDM* genes in *A. baumannii* [110].

A very recent study showed experimental evidence of the horizontal transfer of the Tn125 transposon carrying the *blaNDM-1* gene by transduction from a carbapenem-resistant *A. baumannii* clinical strain (R2090) to a carbapenem-susceptible *A. baumannii* strain. The authors have excluded the involvement of the other three HGT mechanisms. The *blaNDM-1* gene was chromosomally located and flanked by two different insertion elements (IS*Aba125* and IS*CR21*) that might explain the translocation of the gene into the strain. By full sequencing, it was possible to observe that this strain carried three intact prophages in the chromosome and it was suggested that activation of one of these prophages contributed to the transduction; nonetheless, it still remains to be tested if the phages detected are active [111]. So far, this is the first study demonstrating the possible involvement of these mobile elements in the dissemination of carbapenem resistance genes. There are about 20 *A. baumannii* phages described [161] and thus, bacteriophages may indeed contribute to the resistance evolution of *A. baumannii* under antibiotic selective pressure.

6.3. Mechanisms Involved in the Movement and Dissemination of Class A β-Lactamases

6.3.1. KPC-Type

KPC-type carbapenemases are rarely found in *Acinetobacter* spp. These beta-lactamases were identified for the first time in 3.4% (10/274) of clinical multidrug-resistant *A. calcoaceticus-baumannii* complex collected in 2009 in Puerto Rico. Sequencing of the *blaKPC* gene revealed the variants *blaKPC-3* in seven isolates, *blaKPC-4, blaKPC-2* and a new variant *blaKPC-10* in one isolate each [162]. A subsequent study identified 41 *A. baumannii* isolates with the *blaKPC* gene (the variant was not identified) [163]. Identification of the genetic background of *blaKPC-3* in *A. baumannii* demonstrated that it was embedded into Tn4401b located in the chromosome within a 26.5 kb fragment, which included a KQ-like element similar to one described in a K. *pneumoniae* plasmid. This data suggests the acquisition of *blaKPC-3* due to an IS*Ecp1* transposition event [112]. Very recently, whole genome sequencing revealed that the *blaKPC-2* gene of *A. baumannii* (Puerto Rico), assigned to the international ST2 clone, was identified on a new truncated version of transposon Tn4401e (tentatively named Tn4401h), located in the chromosome within an IncA/C plasmid fragment derived from an *Enterobacteriaceae*, probably due to the insertion sequence IS26 [113]. This finding in the widely disseminated ST2 clone suggests further dissemination of *blaKPC-2* in this species.

A study conducted in an Iranian Burn Care Center also identified the *blaKPC* gene in *A. baumannii* isolates but gene transfer was not demonstrated [164].
6.3.2. GES-Type

The GES enzymes are classified as extended-spectrum β-lactamases (ESBLs). However, some variants can act as carbapenemases [165]. Different levels of resistance or reduced susceptibility to carbapenems are observed with different variants [114,115,166]. Thirty-one blaGES gene variants have been described so far [151]; only six have been reported in A. baumannii [2,167] (GenBank accession number NG_049127).

The first blaGES gene reported in A. baumannii was the blaGES-11, which was present as a gene cassette in a class 1 integron; this mobile element was embedded into a plasmid and transfer by conjugation between two A. baumannii isolates was observed [114]. The blaGES gene are embedded into class 1 integrons [116–118] and the majority are plasmid-located [115,116,119]. Nonetheless, chromosomal location has also been reported [116]. Transfer of the blaGES-encoding plasmid by conjugation between A. baumannii has been shown [115,117,119] but transfer to E. coli has failed [115].

The high GC content of the blaGES-11 gene as compared with the A. baumannii genome [114] can be seen as evidence of a different original source for this gene. The occurrence of HGT has also been suggested due to the presence of the same blaGES gene in A. baumannii isolates belonging to different genotypes [167,168].

7. Conclusions

The fast increase of antimicrobial resistance in the last few decades has shown the remarkable ability of the genomic plasticity of Gram-negative bacteria, leading to the ineffective control of many infectious diseases and to a global public health problem of unexpected magnitude. The emergence and dissemination of antimicrobial resistance is an ample evidence of the biological response to the enhanced exposure to toxic molecules and dynamic genetic flux among bacteria. Mutations and lateral gene transfer mechanisms are the key for bacteria genome evolution and adaptation to multiple environments. Members of the Acinetobacter genus are considered environmental bacteria. For unclear reasons, A. baumannii emerged as an important nosocomial opportunistic pathogen. Not being a normal colonizer of non-hospitalized individuals, its reservoir remains unknown. Still considered a low virulence pathogen, infecting mostly immune-debilitated hosts, it acquired enormous clinical relevance when linked to the fast acquisition of resistance to the majority of antibiotic classes, including the last therapeutic resort antimicrobials, such as carbapenems. Since the 1980s, the carbapenems were seen as a new treatment option for serious resistant infections. However, its high activity has been hindered over time by the increase of carbapenem resistance. Many isolates of A. baumannii are often resistant to carbapenems and, as in other Gram-negative bacteria, have at their disposal a plethora of resistance mechanisms that may act in synergy. Production of carbapenemases is undoubtedly the most common mechanism of resistance to carbapenems. Indeed, this species produce the intrinsic carbapenemase OXA-51, that despite its low efficient hydrolysis, its expression and activity can be exacerbated by the upstream ISAb1 or work in conjunction with other mechanisms, as efflux pumps, to give carbapenem resistance [169]. Nevertheless, HGT plays an important role, not yet completely understood, in the dissemination of carbapenemase determinants.

A. baumannii seems to have a notorious ability to survive and it can use all the mechanisms of HGT and mobile genetic elements to spread resistance genes (Table 1). Understanding the extent of carbapenem resistance and how its mobilization takes place is essential to control the dissemination of these genes.

As in other Gram-negative bacteria, conjugation appears to have the greatest influence in the spread of carbapenem resistance determinants. Some of the CHDLs are disseminated by conjugative plasmids and the MBL blaNDM gene seems to be often located in different plasmids of diverse sizes. However, most reports associated blaNDM-type with Tn125, suggesting the intracellular “jumping” of the genetic elementintochromosome and to other plasmids of the new host bacteria. Indeed, blaNDM-type inserted in Tn125 has been found integrated in the chromosome [109], supporting...
the idea of the high dynamic of this gene, which might explain its global widespread in diverse genetic platforms.

For the first time, transduction has been recently suggested to occur as a mechanism of the spread of \textit{bla}_{NDM} genes in \textit{A. baumannii} [111]. Not very widely reported, it is obvious that transduction is an important mechanism of lateral gene transfer when analyzing the genomes of diverse bacteria [170]. Moreover, many bacteria strains gained their virulence (production of some toxins) by the integration of stable prophage in their chromosomal DNA [170,171]. Therefore, it is evident that phage-mediated transduction can contribute to the transfer of resistance genes in \textit{A. baumannii}. Nevertheless, phages are generally specific to the bacteria species [172], which might be a limitation for the spread to other species; however, interspecies transfer of genetic material by transduction was observed [173].

Natural transformation is usually an underestimated mechanism of lateral gene transfer. A barrier is that bacteria need to be naturally competent (and probably why it is thought that it occurs at a low frequency), i.e., to have protein-encoded genes necessary for the uptake of naked DNA, and then, stable integration in the chromosome (or reconstitution of plasmids in the bacterial cytoplasm) [174]. Some members of \textit{Acinetobacter} spp. are naturally competent. It was demonstrated that integrons carrying the MBL \textit{bla}_{IMP-5} gene can be inserted in the chromosome of \textit{A. baylyi}, a naturally competent species, with a negligible biological cost to the recipient cell [97]. Some MBLs, especially from the IMP- and VIM-type families, are part of integrons and many of these isolates do not carry plasmids, suggesting that conjugation is not the involved mechanism (unless they lost the plasmid after transposition to the chromosome). IMP and VIM were the first metallo carbapenemases to be described and despite the increasing number of variants since then, they are not widely spread in \textit{A. baumannii}. Natural transformation may contribute to their dissemination, even if at an initially low rate, which might be followed by high frequency dissemination [97]. This could explain the movement of integrons in the environment among diverse species [175,176] but not in clinical settings. However, recently clinical \textit{A. baumannii} [57,58] and \textit{A. nosocomialis} [177,178] strains were reported as naturally competent in very specific conditions, raising the hypothesis of a role of natural transformation in the resistance dissemination among clinical bacteria. Interestingly, this feature does not appear to be present in all members of the species or be characteristic of a clonal lineage of \textit{A. baumannii}. Moreover, experimental conditions have a critical impact on the acquisition of foreign DNA [58,179]. Nevertheless, this is a mechanism that deserves to be explored with clinical strains and specifically what environmental conditions might influence the acquisition of naked exogenous DNA.

Another unusual reported HGT mechanism is related with the production of OMVs. The mechanisms of vesicle-mediated DNA delivery are not completely understood. A possibility is that competence proteins play a role in the uptake of DNA delivered by OMVs, since vesiculants (transformed cells obtained by vesicle-mediated gene transfer) were not formed with \textit{com} deficient mutants in \textit{A. baylyi}. Interestingly, sub-inhibitory concentrations of gentamicin increased 10 times the transfer of plasmid DNA by OMVs, which might be explained by the altered surface potential by gentamicin-treated population [180].

Recent studies confirmed that \textit{A. baumannii} are able to produce OMVs. It was demonstrated that OMVs released by \textit{A. baumannii} are able to transfer \textit{bla}_{OXA-24} [59], which reinforces the notion that the mediated-OMV mechanism must be taken into account for the dissemination of carbapenemase genes in this pathogenic species. Another study reported the extracellular delivery of OXA-58 in OMVs that shelter cells (even of other species) to the noxious action of carbapenems [145,146]. Not being a way of gene transfer, it is a way of protecting a diverse population of the toxic effects of antibiotics. The mechanisms of delivery from OMVs are still not very clear but the hypothesis suggested by Fulsundar et al. [180] and the recent findings of clinical competent strains, opens new fields of research.

Overall, the dissemination of carbapenemases in \textit{A. baumannii} illustrates the complexity of the micro-dynamic flow of genes and their associated mobile genetic elements. Understanding these genetic mechanisms will allow gains and insights into the epidemiology of resistance genes and to predicting its spread, in order to act in the prevention of dissemination of antimicrobial resistance genes.
Acknowledgments: Faculty of Pharmacy of the University of Coimbra and Center for Neurosciences and Cell Biology through “Fundação para a Ciência e a Tecnologia, projecto Estratégico: UID/NEU/04539/2013”.

Author Contributions: The authors contribute equally to the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Thomas, C.M.; Nielsen, K.M. Mechanisms of, and barriers to, horizontal gene transfer between bacteria. Nat. Rev. Microbiol. 2005, 3, 711–721. [CrossRef] [PubMed]
2. Zhao, W.H.; Hu, Z.Q. Acinetobacter: A potential reservoir and dispenser for beta-lactamases. Crit. Rev. Microbiol. 2012, 38, 30–51. [CrossRef] [PubMed]
3. Evans, B.A.; Amyes, S.G. OXA beta-lactamases. Clin. Microbiol. Rev. 2014, 27, 241–263. [CrossRef] [PubMed]
4. Poirel, L.; Naas, T.; Nordmann, P. Diversity, epidemiology, and genetics of class D beta-lactamases. Antimicrob. Agents Chemother. 2010, 54, 24–38. [CrossRef] [PubMed]
5. Gombac, F.; Riccio, M.L.; Rossolini, G.M.; Lagatolla, C.; Tonin, E.; Monti-Bragadin, C.; Lavenia, A.; Dolzani, L. Molecular characterization of integrons in epidemiologically unrelated clinical isolates of Acinetobacter baumannii from Italian hospitals reveals a limited diversity of gene cassette arrays. Antimicrob. Agents Chemother. 2002, 46, 3665–3668. [CrossRef] [PubMed]
6. Dijkshoorn, L.; Nemec, A.; Seifert, H. An increasing threat in hospitals: Multidrug-resistant Acinetobacter baumannii. Nat. Rev. Microbiol. 2007, 5, 939–951. [CrossRef] [PubMed]
7. Pendleton, J.N.; Gorman, S.P.; Gilmore, B.F. Clinical relevance of the ESKAPE pathogens. Expert Rev. Anti Infect. Ther. 2013, 11, 297–308. [CrossRef] [PubMed]
8. Wendt, C.; Dietze, B.; Dietz, E.; Ruden, H. Survival of Acinetobacter baumannii on dry surfaces. J. Clin. Microbiol. 1997, 35, 1394–1397. [PubMed]
9. 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. [PubMed]
10. Da Silva, G.J. Resistência aos Antibióticos Beta-Lactâmicos em Isolados Clínicos de Acinetobacter spp. Caracterização Molecular de Novas Carbapenemases, IMP-5 e OXA-33, e Estudo Clonal Entre os Isolados Resistentes ao Imipenemo. Ph.D. Thesis, University of Coimbra, Coimbra, Portugal, December 2002.
11. Da Silva, G.; Dijkshoorn, L.; van der Reijden, T.; van Strijen, B.; Duarte, A. Identification of widespread, closely related Acinetobacter baumannii isolates in Portugal as a subgroup of European clone II. Clin. Microbiol. Infect. 2007, 13, 190–195. [CrossRef] [PubMed]
12. Da Silva, G.J.; Mendonca, N.; Batista, G.; Duarte, A. Sequence types of Portuguese carbapenem-resistant Acinetobacter baumannii isolates collected over 10 years. J. Antimicrob. Chemother. 2010, 65, 2254–2256. [CrossRef] [PubMed]
13. Da Silva, G.J.; Quinteira, S.; Bertolo, E.; Sousa, J.C.; Gallego, L.; Duarte, A.; Peixe, L. Long-term dissemination of an OXA-40 carbapenemase-producing Acinetobacter baumannii clone in the Iberian Peninsula. J. Antimicrob. Chemother. 2004, 54, 255–258. [CrossRef] [PubMed]
14. Visca, P.; Seifert, H.; Towner, K.J. Acinetobacter infection—An emerging threat to human health. IUBMB Life 2011, 63, 1048–1054. [CrossRef] [PubMed]
15. Kempf, M.; Rolain, J.M. Emergence of resistance to carbapenems in Acinetobacter baumannii in Europe: Clinical impact and therapeutic options. Int. J. Antimicrob. Agents 2012, 39, 105–114. [CrossRef] [PubMed]
16. Jeannot, K.; Diancourt, L.; Vaux, S.; Thouinourez, M.; Ribeiro, A.; Coignard, B.; Courvalin, P.; Brisse, S. Molecular epidemiology of carbapenem non-susceptible Acinetobacter baumannii in France. PLoS ONE 2014, 9, e115452. [CrossRef] [PubMed]
17. Da Silva, G.J.; van der Reijden, T.; Domínguez, S.; Mendonca, N.; Petersen, K.; Dijkshoorn, L. Characterization of a novel international clonal complex (CC32) of Acinetobacter baumannii with epidemic potential. Epidemiol. Infect. 2014, 142, 1545–1558. [CrossRef] [PubMed]
18. Sunenshine, R.H.; Wright, M.O.; Maragakis, L.L.; Harris, A.D.; Song, X.; Hebden, J.; Cosgrove, S.E.; Anderson, A.; Carnell, J.; Jernigan, D.B.; et al. Multidrug-resistant Acinetobacter infection mortality rate and length of hospitalization. Emerg. Infect. Dis. 2007, 13, 97–103. [CrossRef] [PubMed]
19. Park, S.Y.; Choo, J.W.; Kwon, S.H.; Yu, S.N.; Lee, E.J.; Kim, T.H.; Choo, E.J.; Jeon, M.H. Risk factors for mortality in patients with Acinetobacter baumannii bacteremia. Infect. Chemother. 2013, 45, 325–330. [CrossRef] [PubMed]
20. Falagas, M.E.; Kasiakou, S.K. Colistin: The revival of polymyxins for the management of multidrug-resistant Gram-negative bacterial infections. Clin. Infect. Dis. 2005, 40, 1333–1341. [CrossRef] [PubMed]
21. Doi, Y.; Murray, G.L.; Peleg, A.Y. Acinetobacter baumannii: Evolution of antimicrobial resistance-treatment options. Semin. Respir. Crit. Care Med. 2015, 36, 85–98. [PubMed]
22. Bonnin, R.A.; Nordmann, P.; Poirel, L. Screening and deciphering antibiotic resistance in Acinetobacter baumannii: A state of the art. Expert Rev. Anti Infect. Ther. 2013, 11, 571–583. [CrossRef] [PubMed]
23. Nordmann, P.; Dortet, L.; Poirel, L. Carbapenem resistance in Enterobacteriaceae: Here is the storm! Trends Mol. Med. 2012, 18, 263–272. [CrossRef] [PubMed]
24. Limansky, A.S.; Mussi, M.A.; Viale, A.M. Loss of a 29-kilodalton outer membrane protein in Acinetobacter baumannii is associated with imipenem resistance. J. Clin. Microbiol. 2002, 40, 4776–4778. [CrossRef] [PubMed]
25. Gehrlein, M.; Leying, H.; Cullmann, W.; Wendt, S.; Opferkuch, W. Imipenem resistance in Acinetobacter baumanii is due to altered penicillin-binding proteins. Anaerobe 2004, 10, 298–304. [CrossRef] [PubMed]
26. Poole, K. Efflux pumps as antimicrobial resistance mechanisms. Ann. Med. 2007, 39, 162–176. [CrossRef] [PubMed]
27. Magnet, S.; Courvalin, P.; Lambert, T. Resistance-nodulation-cell division-type efflux pump involved in aminoglycoside resistance in Acinetobacter baumannii strain BM4454. Antimicrob. Agents Chemother. 2001, 45, 3375–3380. [CrossRef] [PubMed]
28. Marchand, I.; Damier-Piolle, L.; Courvalin, P.; Lambert, T. Expression of the RND-type efflux pump AdeABC in Acinetobacter baumannii is regulated by the AdeRS two-component system. Antimicrob. Agents Chemother. 2004, 48, 3298–3304. [CrossRef] [PubMed]
29. Heritier, C.; Poirel, L.; Lambert, T.; Nordmann, P. Contribution of acquired carbapenem-hydrolyzing oxacillinases to carbapenem resistance in Acinetobacter baumannii. Antimicrob. Agents Chemother. 2005, 49, 3198–3202. [CrossRef] [PubMed]
30. Hu, W.S.; Yao, S.M.; Fung, C.P.; Hsieh, Y.P.; Liu, C.P.; Lin, J.F. An OXA-66/OXA-51-like carbapenemase and possibly an efflux pump are associated with resistance to imipenem in Acinetobacter baumannii. Antimicrob. Agents Chemother. 2007, 51, 3844–3852. [CrossRef] [PubMed]
31. Heritier, C.; Poirel, L.; Fournier, P.E.; Claverie, J.M.; Raoult, D.; Nordmann, P. Characterization of the naturally occurring oxacillinase of Acinetobacter baumannii. Antimicrob. Agents Chemother. 2005, 49, 4174–4179. [CrossRef] [PubMed]
32. Heritier, C.; Poirel, L.; Nordmann, P. Cephalosporinase over-expression resulting from insertion of ISAb1 in Acinetobacter baumannii. Clin. Microbiol. Infect. 2006, 12, 123–130. [CrossRef] [PubMed]
33. Turton, J.F.; Ward, M.E.; Woodford, N.; Kaufmann, M.E.; Pike, R.; Livermore, D.M.; Pitt, T.L. The role of ISAb1 in expression of OXA carbapenemase genes in Acinetobacter baumannii. FEMS Microbiol. Lett. 2006, 258, 72–77. [CrossRef] [PubMed]
34. Chen, T.L.; Lee, Y.T.; Kuo, S.C.; Hsueh, P.R.; Chang, F.Y.; Siu, L.K.; Ko, W.C.; Fung, C.P. Emergence and distribution of plasmids bearing the blaOXA-51-like gene with an upstream ISAb1 in carbapenem-resistant Acinetobacter baumanii isolates in Taiwan. Antimicrob. Agents Chemother. 2010, 54, 4575–4581. [CrossRef] [PubMed]
35. Turton, J.F.; Woodford, N.; Glover, J.; Yarde, S.; Kaufmann, M.E.; Pitt, T.L. Identification of Acinetobacter baumannii by detection of the blaOXA-51-like carbapenemase gene intrinsic to this species. J. Clin. Microbiol. 2006, 44, 2974–2976. [CrossRef] [PubMed]
36. Lee, Y.T.; Turton, J.F.; Chen, T.L.; Wu, R.C.; Chang, W.C.; Fung, C.P.; Chen, C.P.; Cho, W.L.; Huang, L.Y.; Siu, L.K. First identification of blaOXA-51-like in non-baumannii Acinetobacter spp. J. Chemother. 2009, 21, 514–520. [CrossRef] [PubMed]
37. Lee, Y.T.; Kuo, S.C.; Chiang, M.C.; Yang, S.P.; Chen, C.P.; Chen, T.L.; Fung, C.P. Emergence of carbapenem-resistant non-baumannii species of Acinetobacter harboring a blaOXA-51-like gene that is intrinsic to A. baumannii. Antimicrob. Agents Chemother. 2012, 56, 1124–1127. [CrossRef] [PubMed]
38. Nordmann, P.; Poirel, L. Emerging carbapenemases in Gram-negative aerobes. *Clin. Microbiol. Infect.* 2002, 8, 321–331. [CrossRef] [PubMed]

39. Jean, S.S.; Lee, W.S.; Lam, C.; Hsu, C.W.; Chen, R.J.; Hsueh, P.R. Carbapenemase-producing Gram-negative bacteria: Current epidemics, antimicrobial susceptibility and treatment options. *Future Microbiol.* 2015, 10, 407–425. [CrossRef] [PubMed]

40. Meletis, G. Carbapenem resistance: Overview of the problem and future perspectives. *Ther. Adv. Infect. Dis.* 2016, 3, 15–21. [CrossRef] [PubMed]

41. Ambler, R.P. The structure of beta-lactamases. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 1980, 298, 321–331. [CrossRef] [PubMed]

42. Lee, K.; Yum, J.H.; Yong, D.; Lee, H.M.; Kim, H.D.; Docquier, J.D.; Rossolini, G.M.; Chong, Y. Novel acquired metallo-beta-lactamase gene, blagSM1, in a class 1 integron from *Acinetobacter baumannii* clinical isolates from Korea. *Antimicrob. Agents Chemother.* 2005, 49, 4485–4491. [CrossRef] [PubMed]

43. Kim, Y.; Roh, K.H.; Lee, Y.; Chung, H.S.; Yum, J.H.; Yong, D.; Lee, K.; Chong, Y. Clonal change of blagSM1-carrying *Acinetobacter* spp. from 2003 to 2008 in the hospital where it was initially discovered. *Microb. Drug Resist.* 2013, 19, 37–41. [CrossRef] [PubMed]

44. Bush, K. The ABCD’s of beta-lactamase nomenclature. *J. Infect. Chemother.* 2013, 19, 549–559. [CrossRef] [PubMed]

45. Higgins, P.G.; Poirel, L.; Lehmann, M.; Nordmann, P.; Seifert, H. OXA-143, a novel carbapenem-hydrolyzing class D beta-lactamase in *Acinetobacter baumannii*. *Antimicrob. Agents Chemother.* 2009, 53, 5035–5038. [CrossRef] [PubMed]

46. Higgins, P.G.; Perez-Llarena, F.J.; Zander, E.; Fernandez, A.; Bou, G.; Seifert, H. OXA-235, a novel class D beta-lactamase involved in resistance to carbapenems in *Acinetobacter baumannii*. *Antimicrob. Agents Chemother.* 2013, 57, 2121–2126. [CrossRef] [PubMed]

47. Elsherif, R.; Ismail, D.; Elawady, S.; Jastaniah, S.; Al-Masaudi, S.; Harakeh, S.; Karrouf, G. Boronic acid disk diffusion for the phenotypic detection of polymerase chain reaction-confirmed, carbapenem-resistant, gram-negative bacilli isolates. *BMC Microbiol.* 2016, 16, 135. [CrossRef] [PubMed]

48. Von Wintersdorff, C.J.; Penders, J.; van Niekerk, J.M.; Mills, N.D.; Majumder, S.; van Alphen, L.B.; Savelkoul, P.H.; Wolfs, P.F. Dissemination of antimicrobial resistance in microbial ecosystems through horizontal gene transfer. *Front. Microbiol.* 2016, 7, 173. [CrossRef] [PubMed]

49. Bergogne-Berezin, E.; Towner, K.J. *Acinetobacter* spp. as nosocomial pathogens: Microbiological, clinical, and epidemiological features. *Clin. Microbiol. Rev.* 1996, 9, 148–165. [PubMed]

50. Fu, Y.; Jiang, J.; Zhou, H.; Jiang, Y.; Fu, Y.; Yu, Y.; Zhou, J. Characterization of a novel plasmid type and various genetic contexts of blaoXA-58 in *Acinetobacter* spp. from multiple cities in China. *PLoS ONE* 2014, 9, e84680. [CrossRef] [PubMed]

51. Heritier, C.; Dubouix, A.; Poirel, L.; Marty, N.; Nordmann, P. A nosocomial outbreak of *Acinetobacter baumannii* isolates expressing the carbapenem-hydrolysing oxacillinase OXA-58. *J. Antimicrob. Chemother.* 2005, 55, 115–118. [CrossRef] [PubMed]

52. Towner, K.J.; Evans, B.; Villa, L.; Levi, K.; Hamouda, A.; Amyes, S.G.; Carattoli, A. Distribution of intrinsic plasmid replica genes and their association with carbapenem-hydrolyzing class D beta-lactamase genes in European *Acinetobacter baumannii* isolates. *Antimicrob. Agents Chemother.* 2011, 55, 2154–2159. [CrossRef] [PubMed]

53. Poirel, L.; Bercot, B.; Millemann, Y.; Bonnin, R.A.; Pannaux, G.; Nordmann, P. Carbapenemase-producing *Acinetobacter* spp. in Cattle, France. *Emerg. Infect. Dis.* 2012, 18, 522–525. [CrossRef] [PubMed]

54. Merabishvili, M.; Vandenheuvel, D.; Kropinski, A.M.; Mast, J.; de Vos, D.; Verbeken, G.; Noben, J.P.; Lavigne, R.; Vaneechoutte, M.; Pirmay, J.P. Characterization of newly isolated lytic bacteriophages active against *Acinetobacter baumannii*. *PLoS ONE* 2014, 9, e104853. [CrossRef] [PubMed]

55. Shen, G.H.; Wang, J.L.; Wen, F.S.; Chang, K.M.; Kuo, C.F.; Lin, C.H.; Luo, H.R.; Hung, C.H. Isolation and characterization of phikm18p, a novel lytic phage with therapeutics potential against extensively drug resistant *Acinetobacter baumannii*. *PLoS ONE* 2012, 7, e46537. [CrossRef] [PubMed]

56. Vaneechoutte, M.; Young, D.M.; Ornston, L.N.; de Baere, T.; Nemeec, A.; van der Reijden, T.; Carr, E.; Tjernberg, I.; Dijkstra, L. Naturally transformable *Acinetobacter* sp. strain ADP1 belongs to the newly described species *Acinetobacter baylyi*. *Appl. Environ. Microbiol.* 2006, 72, 932–936. [CrossRef] [PubMed]
Microorganisms 2016, 4, 29

76. Lolans, K.; Rice, T.W.; Munoz-Price, L.S.; Quinn, J.P. Multicity outbreak of carbapenem-resistant Acinetobacter baumannii isolates producing the carbapenemase OXA-40. Antimicrob. Agents Chemother. 2006, 50, 2941–2945. [CrossRef] [PubMed]

77. Merino, M.; Acosta, J.; Poza, M.; Sanz, F.; Beceiro, A.; Chaves, F.; Bou, G. OXA-24 carbapenemase gene flanked by XerC/XerD-like recombination sites in different plasmids from different Acinetobacter species isolated during a nosocomial outbreak. Antimicrob. Agents Chemother. 2010, 54, 2724–2727. [CrossRef] [PubMed]

78. Grosso, F.; Quinteira, S.; Poirel, L.; Novais, A.; Peixe, L. Role of common blaOXA-24/OXA-40-carrying platforms and plasmids in the spread of OXA-24/OXA-40 among Acinetobacter species clinical isolates. Antimicrob. Agents Chemother. 2012, 56, 3969–3972. [CrossRef] [PubMed]

79. D’Andrea, M.M.; Giani, T.; D'Arezzo, S.; Capone, A.; Petrosillo, N.; Visca, P.; Luzzaro, F.; Rossolini, G.M. Characterization of pABVA01, a plasmid encoding the OXA-24 carbapenemase from Italian isolates of Acinetobacter baumannii. Antimicrob. Agents Chemother. 2009, 53, 3528–3533. [CrossRef] [PubMed]

80. Tian, G.B.; Adams-Haduch, J.M.; Bogdanovich, T.; Pasculle, A.W.; Quinn, J.P.; Wang, H.N.; Doi, Y. Identification of diverse OXA-40 group carbapenemases, including a novel variant, OXA-160, from Acinetobacter baumannii in Pennsylvania. Antimicrob. Agents Chemother. 2011, 55, 429–432. [CrossRef] [PubMed]

81. Marque, S.; Poirel, L.; Heritier, C.; Brisse, S.; Blasco, M.D.; Filipp, R.; Coman, G.; Naas, T.; Nordmann, P. Regional occurrence of plasmid-mediated carbapenem-hydrolyzing oxacillinase OXA-58 in Acinetobacter spp. in Europe. J. Clin. Microbiol. 2005, 43, 4885–4888. [CrossRef] [PubMed]

82. Chen, T.L.; Wu, R.C.; Shaio, M.F.; Fung, C.P.; Cho, W.L. Acquisition of a plasmid-borne blaOXA-58 gene with an upstream IS1008 insertion conferring a high level of carbapenem resistance to Acinetobacter baumannii. Antimicrob. Agents Chemother. 2008, 52, 2573–2580. [CrossRef] [PubMed]

83. Bertini, A.; Poirel, L.; Mugnier, P.D.; Villa, L.; Nordmann, P.; Carattoli, A. Characterization and PCR-based replicon typing of resistance plasmids in Acinetobacter baumannii. Antimicrob. Agents Chemother. 2010, 54, 4168–4177. [CrossRef] [PubMed]

84. Poirel, L.; Nordmann, P. Genetic structures at the origin of acquisition and expression of the carbapenem-hydrolyzing oxacillinase gene blaOXA-58 in Acinetobacter baumannii. Antimicrob. Agents Chemother. 2006, 50, 1442–1448. [CrossRef] [PubMed]

85. Ravasi, P.; Limansky, A.S.; Rodriguez, R.E.; Viale, A.M.; Mussi, M.A. ISAba825, a functional insertion sequence modulating genomic plasticity and blaOXA-58 expression in Acinetobacter baumannii. Antimicrob. Agents Chemother. 2011, 55, 917–920. [CrossRef] [PubMed]

86. Bertini, A.; Poirel, L.; Bernabeu, S.; Fortini, D.; Villa, L.; Nordmann, P.; Carattoli, A. Multiplicity blaOXA-58 gene as a source of high-level resistance to carbapenems in Acinetobacter baumannii. Antimicrob. Agents Chemother. 2007, 51, 2324–2328. [CrossRef] [PubMed]

87. Girlich, D.; Damaceno, Q.S.; Oliveira, A.C.; Nordmann, P. OXA-253, a variant of the carbapenem-hydrolyzing class D β-lactamase OXA-143 in Acinetobacter baumannii. Antimicrob. Agents Chemother. 2014, 58, 2976–2978. [CrossRef] [PubMed]

88. Cayo, R.; Rodrigues-Costa, F.; Matos, A.P.; Carvalhaes, C.G.; Jove, T.; Gales, A.C. Identification of a new integron harboring blaIMP-10 in carbapenem-resistant Acinetobacter baumannii clinical isolates. Antimicrob. Agents Chemother. 2015, 59, 3687–3689. [CrossRef] [PubMed]

89. Da Silva, G.J.; Correia, M.; Vital, C.; Ribeiro, G.; Sousa, J.C.; Letião, R.; Peixe, L.; Duarte, A. Molecular characterization of blaIMP-5, a new integron-borne metallo-β-lactamase gene from Acinetobacter baumannii nosocomial isolate in Portugal. FEMS Microbiol. Lett. 2002, 215, 33–39. [CrossRef]

90. Riccio, M.L.; Franceschini, N.; Boschi, L.; Caravelli, B.; Cornaglia, G.; Fontana, R.; Amicosante, G.; Rossolini, G.M. Characterization of the metallo-beta-lactamase determinant of Acinetobacter baumannii AC-54/97 reveals the existence of blaIMP allelic variants carried by gene cassettes of different phylogeny. Antimicrob. Agents Chemother. 2000, 44, 1229–1235. [CrossRef] [PubMed]

91. Chu, Y.W.; Azfal-Shah, M.; Houang, E.T.; Palepou, M.I.; Lyon, D.J.; Woodford, N.; Livermore, D.M. IMP-4, a novel metallo-beta-lactamase from nosocomial Acinetobacter spp. collected in Hong Kong between 1994 and 1998. Antimicrob. Agents Chemother. 2001, 45, 710–714. [CrossRef] [PubMed]
Mendes, R.E.; Castanheira, M.; Toleman, M.A.; Sader, H.S.; Jones, R.N.; Walsh, T.R. Characterization of an integron carrying blaoIMP-1 and a new aminoglycoside resistance gene, aac(6’)-31, and its dissemination among genetically unrelated clinical isolates in a Brazilian hospital. *Antimicrob. Agents Chemother.* 2007, 51, 2611–2614. [CrossRef] [PubMed]

Liu, S.Y.; Lin, J.Y.; Chu, C.; Su, L.H.; Lin, T.Y.; Chiu, C.H. Integron-associated imipenem resistance in *Acinetobacter baumannii* isolated from a regional hospital in Taiwan. *Int. J. Antimicrob. Agents* 2006, 27, 81–84. [CrossRef] [PubMed]

Wu, T.L.; Ma, L.; Chang, J.C.; Su, L.H.; Chu, C.; Leu, H.S.; Siu, L.K. Variable resistance patterns of integron-associated multidrug-resistant *Acinetobacter baumannii* isolates in a surgical intensive care unit. *Microb. Drug Resist.* 2004, 10, 292–299. [CrossRef] [PubMed]

Domíngues, S.; Nielsen, K.M.; da Silva, G.J. The blaoIMP-1-carrying integron in a clinical *Acinetobacter baumannii* strain is flanked by miniature inverted-repeat transposable elements (MITEs). *J. Antimicrob. Chemother.* 2011, 66, 2667–2668. [CrossRef] [PubMed]

Domíngues, S.; Toleman, M.A.; Nielsen, K.M.; da Silva, G.J. Identical miniature inverted repeat transposable elements (MITEs) flanks class 1 integrons in clinical isolates of *Acinetobacter* spp. *J. Clin. Microbiol.* 2013, 51, 2382–2384. [CrossRef] [PubMed]

Domíngues, S.; Harms, K.; Fricke, W.F.; Johnsen, P.J.; da Silva, G.J.; Nielsen, K.M. Natural transformation facilitates transfer of transposons, integrons and gene cassettes between bacterial species. *PLoS Pathog.* 2012, 8, e1002837. [CrossRef] [PubMed]

Tsakris, A.; Ikonomidou, A.; Pournaras, S.; Tzouvelekis, L.S.; Sofianou, D.; Legakis, N.J.; Maniatis, A.N. VIM-1 metallo-beta-lactamase in *Acinetobacter baumannii*. *Emerg. Infect. Dis.* 2006, 12, 981–983. [CrossRef] [PubMed]

Huang, I.Y.; Chen, T.L.; Lu, P.L.; Tsai, C.A.; Cho, W.L.; Chang, F.Y.; Fung, C.P.; Siu, L.K. Dissemination of multidrug-resistant, class 1 integron-carrying *Acinetobacter baumannii* isolates in Taiwan. *Clin. Microbiol. Infect.* 2008, 14, 1010–1019. [CrossRef] [PubMed]

Yum, J.H.; Yi, K.; Lee, H.; Yong, D.; Lee, K.; Kim, J.M.; Rossolini, G.M.; Chong, Y. Molecular characterization of metallo-beta-lactamase-producing *Acinetobacter baumannii* and *Acinetobacter* genomospecies 3 from Korea: Identification of two new integrons carrying the blaoVIM-2 gene cassettes. *J. Antimicrob. Chemother.* 2002, 49, 837–840. [CrossRef] [PubMed]

Loli, A.; Tzouvelekis, L.S.; Gianneli, D.; Tzelepi, E.; Miriagou, V. Outbreak of *Acinetobacter baumannii* with chromosomally encoded VIM-1 undetectable by imipenem-EDTA synergy tests. *Antimicrob. Agents Chemother.* 2008, 52, 1894–1896. [CrossRef] [PubMed]

Tsakris, A.; Ikonomidou, A.; Poulou, A.; Spanakis, N.; Vrizas, D.; Diomidous, M.; Pournaras, S.; Markou, F. Clusters of imipenem-resistant *Acinetobacter baumannii* clones producing different carbapenemases in an intensive care unit. *Clin. Microbiol. Infect.* 2008, 14, 588–594. [CrossRef] [PubMed]

Wailan, A.M.; Sidjabat, H.E.; Yam, W.K.; Alikhan, N.F.; Petty, N.K.; Sartor, A.L.; Williamson, D.A.; Forde, B.M.; Schembri, M.A.; Beatson, S.A.; et al. Mechanisms involved in acquisition of blaNDM-1 genes by IncA/C2 and IncFIIY plasmids. *Antimicrob. Agents Chemother.* 2016, 60, 4082–4088. [CrossRef] [PubMed]

Huang, Y.M.; Zhong, L.L.; Zhang, X.F.; Hu, H.T.; Li, Y.Q.; Yang, X.R.; Peng, L.Q.; Huang, X.; Tian, G.B. NDM-1-producing *Citrobacter freundii*, *Escherichia coli*, and *Acinetobacter baumannii* identified from a single patient in China. *Antimicrob. Agents Chemother.* 2015, 59, 5073–5077. [CrossRef] [PubMed]

Pillonetto, M.; Arend, L.; Vespero, E.C.; Pelisson, M.; Chaqas, T.P.; Carvalho-Assef, A.P.; Asensi, M.D. First report of NDM-1-producing *Acinetobacter baumannii* sequence type 25 in Brazil. *Antimicrob. Agents Chemother.* 2014, 58, 7592–7594. [CrossRef] [PubMed]

Poiriel, L.; Schrenzel, J.; Cherkauer, O.; Bernabeu, S.; Renzi, G.; Nordmann, P. Molecular analysis of NDM-1-producing enterobacterial isolates from Geneva, Switzerland. *J. Antimicrob. Chemother.* 2011, 66, 1730–1733. [CrossRef] [PubMed]

Zhang, W.J.; Lu, Z.; Schwarz, S.; Zhang, R.M.; Wang, X.M.; Si, W.; Yu, S.; Chen, L.; Liu, S. Complete sequence of the blaoNDM-1-carrying plasmid pNDM-AB from *Acinetobacter baumannii* of food animal origin. *J. Antimicrob. Chemother.* 2013, 68, 1681–1682. [CrossRef] [PubMed]

Bonnin, R.A.; Poiriel, L.; Naas, T.; Pirs, M.; Seme, K.; Schrenzel, J.; Nordmann, P. Dissemination of New Delhi metallo-beta-lactamase-1-producing *Acinetobacter baumannii* in Europe. *Clin. Microbiol. Infect.* 2012, 18, E362–E365. [CrossRef] [PubMed]
109. Decousser, J.W.; Jansen, C.; Nordmann, P.; Emirian, A.; Bonnin, R.A.; Anais, L.; Merle, J.C.; Poirel, L. Outbreak of NDM-1-producing Acinetobacter baumannii in France, January to May 2013. Euro Surveill. 2013, 18, 2–5. [CrossRef] [PubMed]

110. Poirel, L.; Bonnin, R.A.; Boulanger, A.; Schrenzel, J.; Kaase, M.; Nordmann, P. Tn125-related acquisition of blaNDM-like genes in Acinetobacter baumannii. Antimicrob. Agents Chemother. 2012, 56, 1087–1089. [CrossRef] [PubMed]

111. Krahn, T.; Wibberg, D.; Maus, I.; Winkler, A.; Bontront, S.; Sczyrba, A.; Nordmann, P.; Pühler, A.; Poirel, L.; Schlüter, A. Intraspecies transfer of the chromosomally encoded Acinetobacter baumannii blaNDM-1 carbapenemase gene. Antimicrob. Agents Chemother. 2016, 60, 3032–3040. [CrossRef] [PubMed]

112. Martinez, T.; Vazquez, G.J.; Aquino, E.E.; Martinez, I.; Robledo, I.E. Molecular characterization of carbapenem-resistant Acinetobacter baumannii. Antimicrob. Agents Chemother. 2012, 56, 1087–1089. [CrossRef] [PubMed]

113. Krahn, T.; Wibberg, D.; Maus, I.; Winkler, A.; Bontront, S.; Sczyrba, A.; Nordmann, P.; Pühler, A.; Poirel, L.; Schlüter, A. Intraspecies transfer of the chromosomally encoded Acinetobacter baumannii blaNDM-1 carbapenemase gene. Antimicrob. Agents Chemother. 2016, 60, 3032–3040. [CrossRef] [PubMed]

114. Moubareck, C.; Bremont, S.; Conroy, M.C.; Courvalin, P.; Lambert, T. GES-11, a novel integron-associated GES variant in Acinetobacter baumannii. J. Med. Microbiol. 2009, 58, 3579–3581. [CrossRef] [PubMed]

115. Poirel, L.; Bonnin, R.A.; Boulanger, A.; Schrenzel, J.; Kaase, M.; Nordmann, P.; Pühler, A.; Poirel, L.; Schlüter, A. Intraspecies transfer of the chromosomally encoded Acinetobacter baumannii blaNDM-1 carbapenemase gene. Antimicrob. Agents Chemother. 2016, 60, 3032–3040. [CrossRef] [PubMed]

116. Karah, N.; Giske, C.G.; Sundsfjord, A.; Samuelsen, O. A diversity of OXA-carbapenemases and class 1 integrons among carbapenem-resistant Acinetobacter baumannii clinical isolates from Sweden belonging to different international clonal lineages. Microb. Drug Resist. 2011, 17, 545–549. [CrossRef] [PubMed]

117. Charfi-Kessis, K.; Mansour, W.; Ben Haj Khalifa, A.; Mastouri, M.; Nordmann, P.; Aouni, M.; Poirel, L. Multidrug-resistant Acinetobacter baumannii strains carrying the blaOXA-23 and the blagES-11 genes in a neonatology center in Tunisia. Microb. Pathog. 2014, 74, 20–24. [CrossRef] [PubMed]

118. Bogaerts, P.; Naas, T.; El Garch, F.; Deplano, A.; Delaire, T.; Huang, T.D.; Lissoir, B.; Nordmann, P.; Glupczynski, Y. GES extended-spectrum beta-lactamases in Acinetobacter baumannii isolates in Belgium. Antimicrob. Agents Chemother. 2010, 54, 4872–4878. [CrossRef] [PubMed]

119. Moubareck, C.; Bremont, S.; Conroy, M.C.; Courvalin, P.; Lambert, T. GES-11, a novel integron-associated GES variant in Acinetobacter baumannii. Antimicrob. Agents Chemother. 2009, 53, 3579–3581. [CrossRef] [PubMed]

120. Poirel, L.; Schlüter, A. Intraspecies transfer of the chromosomally encoded Acinetobacter baumannii blaNDM-1 carbapenemase gene. Antimicrob. Agents Chemother. 2016, 60, 3032–3040. [CrossRef] [PubMed]

121. Bogaerts, P.; Naas, T.; El Garch, F.; Deplano, A.; Delaire, T.; Huang, T.D.; Lissoir, B.; Nordmann, P.; Glupczynski, Y. GES extended-spectrum beta-lactamases in Acinetobacter baumannii isolates in Belgium. Antimicrob. Agents Chemother. 2010, 54, 4872–4878. [CrossRef] [PubMed]

122. Poirel, L.; Marque, S.; Heritier, C.; Segonds, C.; Chabanon, G.; Nordmann, P. OXA-58, a novel class D beta-lactamase involved in resistance to carbapenems in Acinetobacter baumannii. J. Antimicrob. Chemother. 2005, 59, 202–208. [CrossRef] [PubMed]

123. Poirel, L.; Figueiredo, S.; Cattoir, V.; Carattoli, A.; Nordmann, P. Acinetobacter radioresistens as a silent source of carbapenem resistance for Acinetobacter spp. Antimicrob. Agents Chemother. 2008, 52, 1252–1256. [CrossRef] [PubMed]

124. Zhou, Z.; Du, X.; Wang, L.; Yang, Q.; Fu, Y.; Yu, Y. Clinical carbapenem-resistant Acinetobacter baylyi strain coharboring blaSIM-1 and blaOXA-23 from China. Antimicrob. Agents Chemother. 2011, 55, 5347–5349. [CrossRef] [PubMed]

125. Zander, E.; Fernandez-Gonzalez, A.; Schleicher, X.; Dammhayn, C.; Kamolvit, W.; Seifert, H.; Higgins, P.G. Worldwide dissemination of acquired carbapenem-hydrolyzing class D beta-lactamases in Acinetobacter spp. other than Acinetobacter baumannii. Int. J. Antimicrob. Agents 2014, 43, 375–377. [CrossRef] [PubMed]
126. Adams-Haduch, J.M.; Paterson, D.L.; Sidjabat, H.E.; Pascullle, A.W.; Potoski, B.A.; Muto, C.A.; Harrison, L.H.; Doi, Y. Genetic basis of multidrug resistance in Acinetobacter baumannii clinical isolates at a tertiary medical center in Pennsylvania. Antimicrob. Agents Chemother. 2008, 52, 3837–3843. [CrossRef] [PubMed]

127. La, M.V.; Jureen, R.; Lin, R.T.; Teo, J.W. Unusual detection of an Acinetobacter class D carbapenemase gene, blaOXA-23, in a clinical Escherichia coli isolate. J. Clin. Microbiol. 2014, 52, 3822–3823. [CrossRef] [PubMed]

128. Osterblad, M.; Karah, N.; Halkilahti, J.; Sarkkinen, H.; Uhlin, B.E.; Jalava, J. Rare detection of the Acinetobacter class D carbapenemase blaOXA-23 gene in Proteus mirabilis. Antimicrob. Agents Chemother. 2016, 60, 3243–3245. [CrossRef] [PubMed]

129. Bonnet, R.; Marchandin, H.; Canal, C.; Sirot, D.; Labia, R.; de Champs, C.; Jumas-Bilak, E.; Sirot, J. Characterization of chromosome-encoded class D beta-lactamase OXA-23 in Proteus mirabilis. Antimicrob. Agents Chemother. 2002, 46, 2004–2006. [CrossRef] [PubMed]

130. Liu, L.L.; Ji, S.J.; Ruan, Z.; Fu, Y.; Fu, Y.Q.; Wang, Y.F.; Yu, Y.S. Dissemination of blaOXA-23 in Acinetobacter spp. in China: Main roles of conjugative plasmid pAZJ221 and transposon Tn2009. Antimicrob. Agents Chemother. 2015, 59, 1998–2005. [CrossRef] [PubMed]

131. Bou, G.; Oliver, A.; Martinez-Beltrán, J. OXA-24, a novel class D beta-lactamase with carbapenemase activity in an Acinetobacter baumannii clinical strain. Antimicrob. Agents Chemother. 2006, 50, 2280. [CrossRef]

132. Mosqueda, N.; Gato, E.; Roca, I.; Lopez, M.; de Alegría, C.R.; Fernandez Cuenca, F.; Martinez-Martinez, L.; Pachon, J.; Cisneros, J.M.; Rodriguez-Bano, J.; et al. Characterization of plasmids carrying the blaOX-24/40 carbapenemase gene and the genes encoding the AbkA/AbkB proteins of a toxin/antitoxin system. J. Antimicrob. Chemother. 2014, 69, 2629–2633. [CrossRef] [PubMed]

133. Lee, K.; Kim, M.N.; Choi, T.Y.; Cho, S.E.; Lee, S.; Whang, D.H.; Yong, D.; Chong, Y.; Woodford, N.; Livermore, D.M.; et al. Wide dissemination of OXA-type carbapenemases in clinical Acinetobacter spp. isolates from South Korea. Int. J. Antimicrob. Agents 2009, 33, 520–524. [CrossRef] [PubMed]

134. Quinteiro, S.; Grosso, F.; Ramos, H.; Peixe, L. Molecular epidemiology of imipenem-resistant Acinetobacter haemolyticus and Acinetobacter baumannii isolates carrying plasmid-mediated OXA-40 from a Portuguese hospital. Antimicrob. Agents Chemother. 2007, 51, 3465–3466. [CrossRef] [PubMed]

135. Sevillano, E.; Gallego, L.; García-Lobo, J.M. First detection of the OXA-40 carbapenemase in P. aeruginosa isolates, located on a plasmid also found in A. baumannii. Pathol. Biol. (Paris) 2009, 57, 493–495. [CrossRef] [PubMed]

136. Kuehn, M.J.; Kesty, N.C. Bacterial outer membrane vesicles and the host-pathogen interaction. Genes Dev. 2005, 19, 2645–2655. [CrossRef] [PubMed]

137. Kuehn, M.J.; Kesty, N.C. Bacterial outer membrane vesicles and the host-pathogen interaction. Genes Dev. 2005, 19, 2645–2655. [CrossRef] [PubMed]

138. Kuehn, M.J.; Kesty, N.C. Bacterial outer membrane vesicles and the host-pathogen interaction. Genes Dev. 2005, 19, 2645–2655. [CrossRef] [PubMed]

139. Feng, Y.; Yang, P.; Wang, X.; Zong, Z. Characterization of Acinetobacter johnsonii isolate XBB1 carrying nine plasmids and encoding NDM-1, OXA-58 and PER-1 by genome sequencing. J. Antimicrob. Chemother. 2010, 65, 839–841. [CrossRef] [PubMed]

140. Feng, Y.; Yang, P.; Wang, X.; Zong, Z. Characterization of Acinetobacter johnsonii isolate XBB1 carrying nine plasmids and encoding NDM-1, OXA-58 and PER-1 by genome sequencing. J. Antimicrob. Chemother. 2010, 65, 839–841. [CrossRef] [PubMed]

141. Feng, Y.; Yang, P.; Wang, X.; Zong, Z. Characterization of Acinetobacter johnsonii isolate XBB1 carrying nine plasmids and encoding NDM-1, OXA-58 and PER-1 by genome sequencing. J. Antimicrob. Chemother. 2010, 65, 839–841. [CrossRef] [PubMed]

142. Feng, Y.; Yang, P.; Wang, X.; Zong, Z. Characterization of Acinetobacter johnsonii isolate XBB1 carrying nine plasmids and encoding NDM-1, OXA-58 and PER-1 by genome sequencing. J. Antimicrob. Chemother. 2010, 65, 839–841. [CrossRef] [PubMed]

143. Feng, Y.; Yang, P.; Wang, X.; Zong, Z. Characterization of Acinetobacter johnsonii isolate XBB1 carrying nine plasmids and encoding NDM-1, OXA-58 and PER-1 by genome sequencing. J. Antimicrob. Chemother. 2010, 65, 839–841. [CrossRef] [PubMed]

144. Feng, Y.; Yang, P.; Wang, X.; Zong, Z. Characterization of Acinetobacter johnsonii isolate XBB1 carrying nine plasmids and encoding NDM-1, OXA-58 and PER-1 by genome sequencing. J. Antimicrob. Chemother. 2010, 65, 839–841. [CrossRef] [PubMed]
145. Liao, Y.T.; Kuo, S.C.; Chiang, M.H.; Lee, Y.T.; Sung, W.C.; Chen, Y.H.; Chen, T.L.; Fung, C.P. *Acinetobacter baumannii* extracellular OXA-58 is primarily and selectively released via outer membrane vesicles after Sec-dependent periplasmic translocation. *Antimicrob. Agents Chemother.* 2015, 59, 7346–7354. [CrossRef] [PubMed]

146. Liao, Y.T.; Kuo, S.C.; Lee, Y.T.; Chen, C.P.; Lin, S.W.; Shen, L.J.; Fung, C.P.; Cho, W.L.; Chen, T.L. Sheltering effect and indirect pathogenesis of carbapenem-resistant *Acinetobacter baumannii* in polymicrobial infection. *Antimicrob. Agents Chemother.* 2014, 58, 3983–3990. [CrossRef] [PubMed]

147. Antonio, C.S.; Neves, P.R.; Medeiros, M.; Mamizuka, E.M.; Elmor de Araujo, M.R.; Lincopan, N. High prevalence of carbapenem-resistant *Acinetobacter baumannii* carrying the *bla*OXA-143 gene in Brazilian hospitals. *Antimicrob. Agents Chemother.* 2011, 55, 1322–1323. [CrossRef] [PubMed]

148. Espedido, B.A.; Partridge, S.R.; Iredell, J.R.

149. Leite, G.C.; Oliveira, M.S.; Perdigao-Neto, L.V.; Rocha, C.K.; Guimaraes, T.; Rizek, C.; Levin, A.S.; Costa, S.F. Detection of carbapenemase-producing *Acinetobacter baumannii* isolates by use of liquid chromatography-mass spectrometry and matrix-assisted laser desorption ionization-time of flight mass spectrometry. *J. Clin. Microbiol.* 2013, 51, 287–290. [CrossRef] [PubMed]

150. Yamamoto, M.; Nagao, M.; Matsumura, Y.; Hotta, G.; Matsushima, A.; Ito, Y.; Takakura, S.; Ichiyama, S. Regional dissemination of *Acinetobacter* species harbouring metallo-beta-lactamase genes in Japan. *Clin. Microbiol. Infect.* 2013, 19, 729–736.

151. National Center for Biotechnology Information—Beta-Lactamase Data Resources. Available online: http://www.ncbi.nlm.nih.gov/pathogens/beta-lactamase-data-resources/ (accessed on 23 May 2016).

152. Espedido, B.A.; Partridge, S.R.; Iredell, J.R. *bla*IMP-4 in different genetic contexts in *Enterobacteriaceae* isolates from Australia. *Antimicrob. Agents Chemother.* 2008, 52, 2984–2987. [CrossRef] [PubMed]

153. Grosso, F.; Silva, L.; Sousa, C.; Ramos, H.; Quinteira, S.; Peixe, L. Extending the reservoir of *bla*IMP-5: The emerging pathogen *Acinetobacter bereziniae*. *Future Microbiol.* 2015, 10, 1609–1613. [CrossRef] [PubMed]

154. Takahashi, A.; Yomoda, S.; Kobayashi, I.; Okubo, T.; Tsunoda, M.; Iyobe, S. Detection of carbapenemase-producing *Acinetobacter baumannii* in a hospital. *J. Clin. Microbiol.* 2000, 38, 526–529. [PubMed]

155. Zhao, W.H.; Hu, Z.Q. Epidemiology and genetics of VIM-type metallo-beta-lactamases in Gram-negative bacilli. *Future Microbiol.* 2011, 6, 317–333. [CrossRef] [PubMed]

156. INTEGRALL—The Integron Database. Available online: http://integrall.bio.ua.pt/ (accessed on 23 May 2016).

157. Oh, E.J.; Lee, S.; Park, Y.J.; Park, J.J.; Park, K.; Kim, S.I.; Kang, M.W.; Kim, B.K. Prevalence of metallo-beta-lactamase among *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in a Korean university hospital and comparison of screening methods for detecting metallo-beta-lactamase. *J. Microbiol. Methods* 2005, 64, 411–418. [CrossRef]

158. Lee, M.F.; Peng, C.F.; Hsu, H.J.; Chen, Y.H. Molecular characterisation of the metallo-beta-lactamase genes in imipenem-resistant Gram-negative bacteria from a university hospital in southern Taiwan. *Int. J. Antimicrob. Agents* 2008, 32, 475–480. [CrossRef] [PubMed]

159. Pfeifer, Y.; Wilharm, G.; Zander, E.; Wichelhaus, T.A.; Gottig, S.; Hunfeld, K.P.; Seifert, H.; Witte, W.; Higgins, P.G. Molecular characterization of *bla*NDM-1 in an *Acinetobacter baumannii* strain isolated in Germany in 2007. *J. Antimicrob. Chemother.* 2011, 66, 1998–2001. [CrossRef] [PubMed]

160. Espinal, P.; Foirel, L.; Carmeli, Y.; Kaase, M.; Pal, T.; Nordmann, P.; Vila, J. Spread of NDM-2-producing *Acinetobacter baumannii* in the Middle East. *J. Antimicrob. Chemother.* 2013, 68, 1928–1930. [CrossRef] [PubMed]

161. Jeon, J.; D’Souza, R.; Pinto, N.; Ryu, C.M.; Park, J.; Yong, D.; Lee, K. Characterization and complete genome sequence analysis of two *Myovirial* bacteriophages infecting clinical carbapenem-resistant *Acinetobacter baumannii* isolates. *J. Appl. Microbiol.* 2016, 121, 67–77. [CrossRef] [PubMed]

162. Robledo, I.E.; Aquino, E.E.; Sante, M.I.; Santana, J.L.; Otero, D.M.; Leon, C.F.; Vazquez, G.J. Detection of KPC in *Acinetobacter* spp. in Puerto Rico. *Antimicrob. Agents Chemother.* 2010, 54, 1354–1357. [CrossRef] [PubMed]
163. Robledo, I.E.; Aquino, E.E.; Vazquez, G.J. Detection of the KPC gene in Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Acinetobacter baumannii during a PCR-based nosocomial surveillance study in Puerto Rico. *Antimicrob. Agents Chemother.* 2011, 55, 2968–2970. [CrossRef] [PubMed]

164. Azimi, L.; Talebi, M.; Pourshafie, M.R.; Owlia, P.; Rastegar Lari, A. Characterization of carbapenemases in extensively drug resistance Acinetobacter baumannii in a Burn Care Center in Iran. *Int. J. Mol. Cell. Med.* 2015, 4, 46–53. [PubMed]

165. Queenan, A.M.; Bush, K. Carbapenemases: The versatile beta-lactamases. *Clin. Microbiol. Rev.* 2007, 20, 440–458. [CrossRef] [PubMed]

166. Al-Agamy, M.H.; Khalaf, N.G.; Tawfick, M.M.; Shibl, A.M.; El Kholy, A. Molecular characterization of carbapenem-insensitive Acinetobacter baumannii in Egypt. *Int. J. Infect. Dis.* 2014, 22, 49–54. [CrossRef] [PubMed]

167. Cicek, A.C.; Saral, A.; Iraz, M.; Ceylan, A.; Duzgun, A.O.; Peleg, A.Y.; Sandalli, C. OXA- and GES-type beta-lactamases predominate in extensively drug-resistant Acinetobacter baumannii isolates from a Turkish University Hospital. *Clin. Microbiol. Infect.* 2014, 20, 410–415. [CrossRef] [PubMed]

168. Hammoudi, D.; Moubareck, C.A.; Hakime, N.; Houmani, M.; Barakat, A.; Najjar, Z.; Suleiman, M.; Fayad, N.; Sarraf, R.; Sarkis, D.K. Spread of imipenem-resistant Acinetobacter baumannii co-expressing OXA-23 and GES-11 carbapenemases in Lebanon. *Int. J. Infect. Dis.* 2015, 36, 56–61. [CrossRef] [PubMed]

169. Poirel, L.; Nordmann, P. Carbapenem resistance in Acinetobacter baumannii: Mechanisms and epidemiology. *Clin. Microbiol. Infect.* 2006, 12, 826–836. [CrossRef] [PubMed]

170. Canchaya, C.; Fournous, G.; Brussow, H. The impact of prophages on bacterial chromosomes. *Mol. Microbiol.* 2004, 53, 9–18. [CrossRef] [PubMed]

171. Brussow, H.; Canchaya, C.; Hardt, W.D. Phages and the evolution of bacterial pathogens: From genomic rearrangements to lysogenic conversion. *Microbiol. Mol. Biol. Rev.* 2004, 68, 560–602. [CrossRef] [PubMed]

172. Brabban, A.D.; Hite, E.; Callaway, T.R. Evolution of foodborne pathogens via temperate bacteriophage-mediated gene transfer. *Foodb. Pathog. Dis.* 2005, 2, 287–303. [CrossRef] [PubMed]

173. Chen, J.; Novick, R.P. Phage-mediated intergeneric transfer of toxin genes. *Science* 2009, 323, 139–141. [CrossRef] [PubMed]

174. Nielsen, K.M.; Ray, J.L.; Johnsen, P.J. Horizontal gene transfer: Uptake of extracellular DNA by bacteria. In *Encyclopedia of Microbiology*; Shaechter, M., Ed.; Elsevier: Oxford, UK, 2009; pp. 587–596.

175. Stokes, H.W.; Gillings, M.R. Gene flow, mobile genetic elements and the recruitment of antibiotic resistance genes into Gram-negative pathogens. *FEMS Microbiol. Rev.* 2011, 35, 790–819. [CrossRef] [PubMed]

176. Domingues, S.; da Silva, G.J.; Nielsen, K.M. Global dissemination patterns of common gene cassette arrays in class 1 integrons. *Microbiology* 2015, 161, 1313–1337. [CrossRef] [PubMed]

177. Carruthers, M.D.; Harding, C.M.; Baker, B.D.; Bonomo, R.A.; Hujer, K.M.; Rather, P.N.; Munson, R.S., Jr. Draft genome sequence of the clinical isolate Acinetobacter nosocomialis strain M2. *Genome Announc.* 2013, 1, e00906-13. [CrossRef] [PubMed]

178. Harding, C.M.; Tracy, E.N.; Carruthers, M.D.; Rather, P.N.; Actis, L.A.; Munson, R.S., Jr. Acinetobacter baumannii strain M2 produces type IV pili which play a role in natural transformation and twitching motility but not surface-associated motility. *MBio* 2013, 4, e00360–e00313. [CrossRef] [PubMed]

179. Johnsborg, O.; Eldholm, V.; Havarstein, L.S. Natural genetic transformation: Prevalence, mechanisms and function. *Res. Microbiol.* 2007, 158, 767–778. [CrossRef] [PubMed]

180. Fulsundar, S.; Harms, K.; Flaten, G.E.; Johnsen, P.J.; Chopade, B.A.; Nielsen, K.M. Gene transfer potential of outer membrane vesicles of Acinetobacter baumannii and effects of stress on vesiculation. *Appl. Environ. Microbiol.* 2014, 80, 3469–3483. [CrossRef] [PubMed]