



ISSN : 2347 - 2243

Indo - American Journal of Life Sciences and Biotechnology



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Carbapenem Resistance Genes in *Acinetobacter baumannii* From Intensive Care Units

Oliver Treloar¹●, Romain Chastain²●, Wout Peeters³●

¹Associate Professor, Department of Microbiology, Penwith Institute of Applied Microbiology, Penzance, United Kingdom.

²Professor, Department of Medical Microbiology, Perigord Centre for Biomedical Research, Perigueux, France.

³Research Associate, Department of Biotechnology, Ardennes Centre for Genetics, Bastogne, Belgium.

Email: ¹o.treloar@pam.ac.uk, ²r.chastain@pcbr.fr, ³w.peeters@acg-b.be

ORCID: ¹0000-0001-0335-5200, ²0000-0001-1451-2259, ³0000-0001-1893-9006

Received: November 3, 2012 Accepted: March 15, 2013 Published: June 29, 2013

DOI: [10.62644/iajlb.2013.v10.i2.pp19-28](https://doi.org/10.62644/iajlb.2013.v10.i2.pp19-28)

ABSTRACT

Carbapenems have long been the dependable last line against multidrug-resistant *Acinetobacter baumannii*, the Gram-negative bacterium that has settled into intensive care units (ICUs) around the world. That reliability is eroding, and the genes behind the erosion are the subject of this narrative review. It draws on published work on the oxacillinase families, the metallo-beta-lactamases, the insertion sequences that switch resistance genes on, the contribution of efflux and permeability changes, and the clonal lineages that carry all of this between hospitals. No new data are reported, and the title is treated as a topic in the literature, not as a local survey. The evidence shows that resistance rarely rests on a single gene: an intrinsic OXA-51-like enzyme becomes clinically relevant only when an upstream insertion sequence drives it, acquired OXA-23, OXA-24/40 and OXA-58 enzymes add to it, and NDM-1 now threatens to remove the remaining options. Detection is uneven, because phenotypic susceptibility results and gene-based assays answer different questions, and published surveillance is dominated by a few regions and by outbreak reports, which limits how far any pattern can be generalised. The review sets out what a laboratory report should state, what an ICU can reasonably infer from it, and which gaps in the literature matter most.

Keywords: *Acinetobacter baumannii*; Carbapenem resistance; Oxacillinases; Metallo-beta-lactamases; Intensive care unit; Insertion sequences; Narrative review

Citation: Treloar, Chastain and Peeters [2013]. Carbapenem Resistance Genes in *Acinetobacter baumannii* From Intensive Care Units. *Indo-Am. J. Life Sci. Biotechnol.* 10(2):19-28. DOI: [10.62644/iajlb.2013.v10.i2.pp19-28](https://doi.org/10.62644/iajlb.2013.v10.i2.pp19-28)

Article Class: Narrative Review

1. Introduction

For most of the past two decades the carbapenems have been the drugs that clinicians reach for when a Gram-negative infection in a critically ill patient refuses to respond to anything else. *Acinetobacter*

baumannii has made that habit harder to sustain. The organism is an opportunist of the intensive care unit (ICU), where ventilators, catheters and prolonged stays give it plenty to colonise (1, 2), and it has acquired a reputation for resisting almost



every class of antibiotic that is thrown at it (3, 4).

Carbapenem resistance in this species is not one thing. Reviews written within the last several years describe a patchwork of enzymes, regulatory accidents, membrane changes and efflux pumps that vary from hospital to hospital (5, 6). The genes involved are the focus here, because they are what molecular laboratories can actually detect, and because their arrival in a unit often signals something about where the bacterium came from and where it may go next (7, 8).

The title of this article reads like a survey of a single set of ICUs, and the reader should know at the outset that it is nothing of the kind. No local isolates were collected, no genes were sequenced and no patients were studied. What follows is a narrative review of the published literature on carbapenem-resistance genes in *A. baumannii* in critical care, written to explain what is known, how it is measured and where the evidence is thin. The aim is a fair account of what is known, and of what is merely repeated.

The review proceeds from the biology of the organism and its resistance genes to the way they are detected and reported, and then to what ICU teams can reasonably conclude from such reports. Tables and figures are qualitative on purpose. Numbers that differ between regions and years are better taken from the primary surveillance papers than from a summary like this one.

2. Literature Review

2.1 The Organism and Its ICU Niche

Acinetobacter baumannii is a non-fermenting coccobacillus that survives remarkably well in hospitals. It tolerates drying, persists on equipment and bed rails, and spreads on the hands of staff, which together help explain why units that

have had an outbreak struggle to be rid of it (9, 10). Bloodstream surveillance of United States hospitals earlier in the previous decade already placed the genus among the more frequent and more deadly causes of nosocomial sepsis in ICU patients (11).

The clinical picture is dominated by ventilator-associated pneumonia, bloodstream and wound infections, and the attributable burden of resistant strains is difficult to separate from the severity of the patients who acquire them (2, 12). That difficulty is worth keeping in mind later. A gene detected in a very sick population does not, on its own, prove that the gene made the patient sicker. A bacterium that has lived for years on a unit behaves differently from one that has just arrived.

2.2 Oxacillinases: The Dominant Family

Most carbapenem resistance in *A. baumannii* is traced to class D beta-lactamases, the oxacillinases. All isolates of the species carry a chromosomal OXA-51-like gene, and for some years this was treated as a convenient species marker (13). The enzyme hydrolyses carbapenems only weakly, so on its own the gene does not make an isolate resistant; what changes things is an insertion sequence, ISAb₁, that lands upstream of the gene and supplies a strong promoter (14, 15).

Alongside the intrinsic gene sit three acquired groups, usually named for their founding members: OXA-23, OXA-24/40 and OXA-58. The OXA-23 group is the most widely reported and has been found on several continents, often within a transposon (16, 17). The OXA-24/40 group was characterised in outbreak settings (18), and OXA-58 is typically flanked by insertion sequences that influence its expression (19). General reviews of the family make the same point from different angles: the enzymes are



numerous, their carbapenemase activity is modest in vitro, and the clinical effect depends heavily on the genetic setting (20, 21). Table 1 gathers the main determinants.

2.3 Metallo-beta-lactamases and the Arrival of NDM-1

Metallo-beta-lactamases (MBLs) are a different proposition. They use zinc rather than a serine residue at the active site, they hydrolyse nearly all beta-lactams except aztreonam, and they are not inhibited by the usual beta-lactamase inhibitors (22, 25). In *A. baumannii* the IMP, VIM and SIM types have been reported, mostly on integrons, and with a geographic pattern that is hard to describe without leaning on selected reports.

Table 1. Main carbapenem-resistance determinants reported in *Acinetobacter baumannii*.

Determinant	Class	Usual position	Comment
OXA-51-like	D, intrinsic	Chromosome	Weak alone; needs ISAba1 (14, 15)
OXA-23-like	D, acquired	Plasmid or transposon	Most widely reported (16, 17)
OXA-24/40-like	D, acquired	Plasmid	Outbreaks described (18)
OXA-58-like	D, acquired	Plasmid	Flanking insertion sequences (19)
IMP, VIM, SIM	B, metallo	Integrons	Hydrolyse almost all beta-lactams (22)
NDM-1	B, metallo	Plasmid or chromosome	Recent arrival (23, 24)

Note: Qualitative summary of the cited literature; contribution varies by isolate and setting.

The emergence of NDM-1, first described in a *Klebsiella pneumoniae* isolate (26), changed the conversation. Its spread across Enterobacteriaceae was documented quickly (27, 28), and reviews of the NDM family describe a gene that moves readily between species and plasmids (29). Environmental sampling in New Delhi found NDM-1 positive bacteria well beyond the hospital (30). The first reports in *Acinetobacter* followed, including isolates in which NDM-1 appeared together with OXA-23 and an aminoglycoside-resistance gene (23), and a report from China of NDM-1-producing *A. baumannii* (24). These are small numbers of isolates, and caution is appropriate, but the direction of travel is clear.

2.4 Efflux, Permeability and Everything Else

Enzymes are not the whole story. Efflux pumps, loss or reduced production of outer-membrane proteins, and alterations in penicillin-binding proteins can each raise the carbapenem minimum inhibitory concentration, and in many isolates they act together with an oxacillinase (6, 31). The biology behind these changes is less tidy than the biology of a single enzyme, which is partly why routine laboratories seldom look for it.

The practical consequence is that a negative result for a carbapenemase gene does not leave an isolate susceptible. An isolate resistant by susceptibility testing and negative on a targeted panel is often resistant for a reason the panel was never designed to see, and the review literature has long said so (5, 32). Read this way, the absence of a gene in a panel is not evidence that the mechanism is absent.

2.5 Clones, Plasmids and the Mobile Genome

Genes do not travel alone. Population studies with multilocus sequence typing



have shown that most multiresistant isolates cluster in a limited number of lineages, with a few international clones recurring in hospitals on several continents (33, 34). The worldwide picture of carbapenem-resistant lineages, and the differences between regions, has been reviewed several times (7, 8), and European data in particular show how quickly a successful lineage can establish itself (35).

Genome comparison has added the mobile dimension. The first sequenced multidrug-resistant strains carried large islands of resistance genes inserted into the chromosome (36, 37), and the related species *Acinetobacter radioresistens* has been proposed as a silent reservoir of the OXA-23 gene from which other species may have drawn it (38). A resistance gene, in other words, can be moved by the plasmid, the transposon, the insertion sequence or the clone, and reports that say only that the gene was found leave most of that out.

3. Materials and Methods

3.1 Scope

This is a narrative review. It covers carbapenem-resistance determinants in *A. baumannii* that have been described in the context of hospital and ICU infection, with attention to gene families, genetic context, detection methods and population structure. It does not review treatment trials, and it does not attempt a meta-analysis. Because the title could be mistaken for a local study, we state again that no local data are reported.

3.2 Literature Assembly

The sources were assembled informally. No formal systematic search protocol was used, no database search strings were registered and no screening was carried out in duplicate. We began with widely cited reviews of the organism, then followed

their reference lists to the primary reports on individual gene families, and added methodological papers on typing and detection. Only works published on or before the year of this issue were considered. None of these steps is difficult, but each one is easy to skip on a busy unit.

An approach of this kind favours well-known papers and English-language journals, and it will miss unpublished surveillance and regional reports. We say so plainly because the same bias is likely to be present in the literature we draw on.

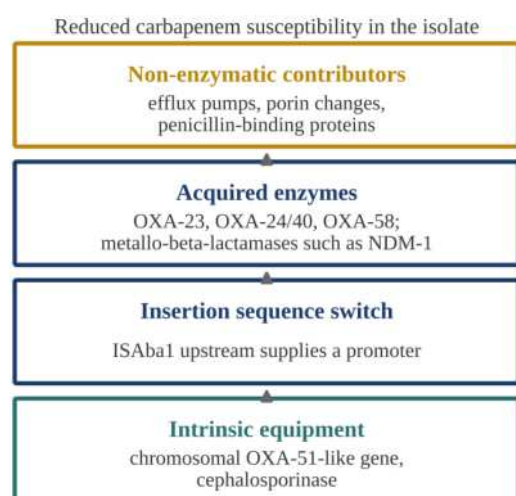
3.3 Appraisal Framework

Each source was read against four plain questions. What exactly was measured, a phenotype or a gene? How were isolates chosen, and how many units or hospitals do they represent? Was the genetic context described, or only the presence of the gene? And do the authors' conclusions go beyond what was measured? Standard definitions of multidrug resistance (39) were used to keep terms consistent, and no scoring system was applied.

4. Results

4.1 How Resistance Layers Up in a Single Isolate

The first finding of the literature is that resistance in a given isolate is usually built from several layers. At the bottom sits the intrinsic equipment of the species: a chromosomal cephalosporinase whose expression is raised by ISAba1 (40), and the OXA-51-like enzyme. Above that come acquired oxacillinases or, more rarely, MBLs, and above those the non-enzymatic contributors, efflux and permeability. Figure 1 sketches this layering. It is a conceptual diagram, not a count, and no isolate necessarily has every layer. The order is for clarity only, and the layers are not equally easy to detect.



schematic, not data; not every isolate has every layer

Figure 1. Layers that combine to produce carbapenem resistance in one isolate (schematic, not data).

Two consequences follow. A change in one layer, for example the acquisition of a plasmid carrying an OXA-23 gene, may add little where another layer is already doing the work, and a great deal where it is not. And because the layers interact, comparing the minimum inhibitory concentrations of two isolates tells us rather little about which genes they carry (5, 14). This is why the same gene can look decisive in one hospital and almost irrelevant in the next.

4.2 Genetic Context Matters More Than Presence

The literature is surprisingly consistent on one point: a gene without its promoter is a bystander. The ISAbal story is the clearest case. OXA-51-like genes are found in every isolate, yet carbapenem resistance appears when ISAbal sits upstream and drives them (14, 15), and similar logic applies to the acquired groups, where flanking insertion sequences and transposon structures control how much enzyme is made (17, 19). A resistance gene that is present but silent is a different problem from one that is expressed.

This is the point at which the reporting of many studies falls short. A paper that records the presence of an OXA gene by PCR, and says nothing of whether it is expressed, can be read in two quite different ways. A fuller description includes the neighbouring elements, the replicon or chromosomal location, and the phenotype of the isolate. Few reports give all three.

4.3 Detection and Reporting

Laboratories answer different questions with different tools, and Table 2 sets them side by side. Susceptibility testing reports the phenotype and is the basis for the formal categories of multidrug, extensive and pandrug resistance (39). Multiplex PCR for the prevalent OXA groups is cheap and repeatable (41), while typing schemes locate an isolate within the population (33), and genome sequencing can in principle give all of it at once (37). A clinician reading a laboratory report wants one thing above all: what does this change for the patient in the bed?

Table 2. What different laboratory approaches can and cannot tell an ICU.

Approach	Answers	Misses
Susceptibility testing	Whether the isolate is resistant now (39)	Which gene is responsible
Multiplex PCR	Presence of prevalent OXA groups (41)	New or rare variants
Insertion sequence mapping	Whether a gene is switched on (14)	Needs extra primers and care
Typing by MLST	Relatedness between isolates (33, 34)	Resistance content
Whole-genome sequencing	Genes, context and lineage (36, 37)	Cost, expertise, phenotype link

Note: Approaches are those described in the cited literature; availability differs between laboratories.



Each approach leaves something out. A panel built around known groups cannot detect a variant that was unknown when the primers were designed, and a typing scheme says nothing about what resistance genes the lineage carries. Reports that combine a phenotype, a targeted gene result and a lineage are more informative than any single one, but they are also the least common. Such differences look small in a single report, yet they decide whether two studies can be compared at all.

Figure 2 summarises, qualitatively, how the main determinants compare on features that matter for an ICU: how readily they are detected, how well they spread between isolates, and how likely they are to remove treatment options. The ratings in the figure are the authors' reading of the cited reviews and not measured values.

	Easy to detect	Moves between isolates	Removes options
OXA-51-like + ISAb1	mid	low	low
OXA-23-like	high	high	mid
OXA-24/40-like	mid	mid	mid
OXA-58-like	mid	mid	mid
IMP / VIM / SIM	mid	mid	high
NDM-1	mid	high	high

schematic of qualitative ratings, not data

Figure 2. Qualitative matrix of determinants against the features that matter in an ICU (schematic, not data).

4.4 What ICU Reports Show, and What They Do Not

Published ICU material falls into recognisable types, shown in Table 3. Outbreak reports are the most vivid and the most numerous; they show how a single clone can enter a unit, expand and persist (9, 18). Regional surveys show which lineages and genes circulate, though

coverage is uneven (7, 8). Single-gene PCR studies are easy to run and easy to compare, but they hide the mechanisms they were not designed to find (41).

Table 3. Patterns in ICU reports and their usual limitations.

Pattern	Meaning	Limitation
Outbreak report	Shows how a clone can move through a unit (9, 18)	Selected, often single-centre
Regional survey	Shows lineages and genes in circulation (7, 8)	Uneven coverage of regions
Single-gene PCR study	Cheap, repeatable (41)	Cannot show new mechanisms
Genome comparison	Reveals islands and mobile elements (36, 37)	Few isolates, mostly outbreak strains

Note: Limitations are those discussed in the cited reviews; they are not attributed to any single study.

Taken as a body, this literature is better at describing the success of particular clones than at estimating how common any mechanism is across ICUs in general. It is dominated by outbreaks and by a handful of well-resourced regions. That is not a criticism of the individual papers; it is a feature of what gets investigated and published. The point is not that a survey is poor, only that its result travels less far than its abstract suggests.

5. Discussion

5.1 Interpretation

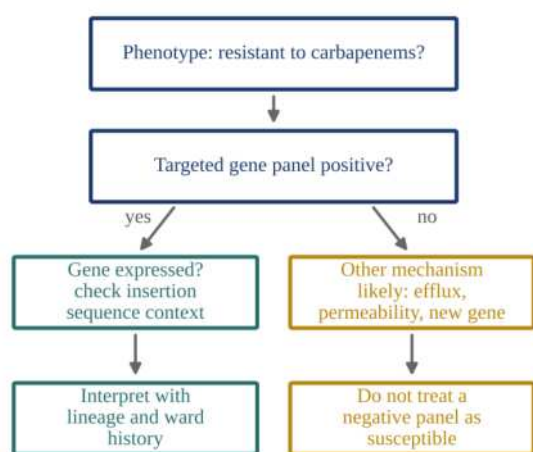
Putting these strands together, the likeliest picture is of a species that has two routes to carbapenem resistance. The first is regulatory: an insertion sequence turns an intrinsic gene from a bystander into a resistance determinant. The second is acquisitive: a plasmid or transposon delivers a new oxacillinase or, increasingly, an MBL. Both routes have been seen repeatedly, and both are strengthened by clonal expansion in



hospitals (3, 4).

For an ICU team receiving a molecular report, Figure 3 sketches a reasoning path. It starts with the phenotype, not the gene: is the isolate resistant to carbapenems, and by which method was that established? It then asks whether a targeted gene was found, and whether a gene that is present has any reason to be expressed. A report that stops at gene presence leaves the second question open, and a negative panel in a resistant isolate should send the reader to other mechanisms, not to reassurance.

The therapeutic consequences are only touched on here. When enzymes remove the carbapenems, clinicians have often fallen back on polymyxins, and those too carry costs and uncertainties (42, 43). Reviews of the management of resistant *Acinetobacter* tend to be cautious, because the quality of the underlying comparative evidence is modest (12, 44).



schematic, not data

Figure 3. Decision sketch for reading a carbapenem-resistance report from an ICU isolate (schematic, not data).

5.2 Limitations

The first limitation is the method. A narrative review without a registered search will over-represent famous papers,

and the choice of what to include rests on the authors' judgement. A second is the age of the evidence: much of it describes the period before the most recent spread of NDM-1, and the position may already have shifted. A third is the unevenness of the source material, with most primary reports coming from a limited set of countries and from outbreak investigations, a limitation noted in several of the reviews cited above (32, 35). Reviews of this kind are more useful when they say where the evidence stops than when they smooth it over.

There is also a deeper problem that no review can fix. Carbapenem resistance is a property of an isolate in a patient in a unit, and what is reported is a property of a sample in a laboratory. The distance between the two is rarely measured.

5.3 Future Work

Three kinds of work would improve matters. Surveillance that records phenotype, gene, genetic context and lineage together, from a wider range of ICUs and countries, would allow genuine comparison (8, 37). Studies that distinguish a silent gene from an expressed one would help clinicians read molecular reports more sensibly. And reports that follow a unit over time, rather than describing a single outbreak, would show how quickly mechanisms replace one another and whether infection-control measures change that pace (9, 10). It is a habit worth keeping even when the answer is expected.

6. Conclusion

Carbapenem resistance in *Acinetobacter baumannii* is the product of layers: an intrinsic gene switched on by an insertion sequence, acquired oxacillinases carried on mobile elements, a growing number of metallo-beta-lactamases and a background of efflux and permeability changes. Clonal spread within and between ICUs moves



them around. The literature describes these pieces well but is weaker at telling us how often each occurs in ICUs overall.

For the practitioner the message is a cautious one. Read the phenotype first, ask whether the gene found is likely to be expressed, and do not take a negative panel as proof of susceptibility. These points apply with equal force to other Gram-negative pathogens, not only to *Acinetobacter*. For the researcher, the opening is for surveillance that is broader, more complete in its reporting and less dependent on outbreaks.

7. Acknowledgements

The authors thank colleagues who commented on earlier drafts of this review.

8. Funding

This work received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

9. Conflict of Interest

The authors declare no conflict of interest.

10. Author Contributions

O.T. conceived the review and wrote the sections on resistance genes and mobile elements. R.C. wrote the sections on clinical microbiology and detection. W.P. wrote the sections on genetics and typing. All authors revised the manuscript and approved the final version.

11. Ethics Statement

This is a review of published literature. No patients or isolates were studied and no ethical approval was required.

12. Data Availability

No new data were generated. All sources are cited in the reference list.

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