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REVIEW

Combating Multidrug-Resistant *Acinetobacter baumannii*: Insights from Japan, with Global Relevance

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Abstract: *Acinetobacter baumannii* is a non-fermentative Gram-negative bacillus known for its environmental persistence, rapid acquisition of multidrug resistance (MDR), and high outbreak potential. The 2024 World Health Organization priority pathogen list places it in the highest "Critical" tier. This review summarizes definitions, resistance mechanisms, epidemiology in Japan and abroad, diagnostic approaches, infection control, and current or emerging therapies. Carbapenem resistance is largely mediated by OXA-type carbapenemases, often together with additional mechanisms. While isolates in Japan still show comparatively high susceptibility to key agents, many Asia-Pacific and Latin American settings report substantially higher resistance. Phenotypic and molecular diagnostic tools remain essential for outbreak control. Despite the availability of several established and novel agents, no universally accepted regimen exists, and combination therapy is often necessary. This observed gap in resistance levels may reflect variation in surveillance intensity, infection control policies, and antimicrobial stewardship. Appreciating these contextual differences can inform countries that are beginning to face increasing MDR *A. baumannii* burdens and support the design of locally applicable preparedness strategies.

Keywords: carbapenemase, antimicrobial stewardship, sulbactam/durlobactam, cefiderocol, infection control, global health

Introduction

Multidrug-resistant (MDR) *Acinetobacter baumannii* has emerged as a critical healthcare-associated pathogen worldwide, particularly in intensive care units and among immunocompromised patients.[1] Its ability to survive in harsh environments, resist disinfectants, and acquire a wide array of antimicrobial resistance mechanisms has led to persistent outbreaks and limited therapeutic options in many regions, including Southeast Asia, Latin America, and Southern Europe.[2] These infections, particularly ventilator-associated pneumonia and bloodstream infections, are frequently associated with high mortality and prolonged hospital stays, creating a substantial burden on intensive-care settings. Global health authorities, including the World Health Organization (WHO), now classify MDR *A. baumannii* as a top-tier threat, call for improved surveillance, infection prevention, and treatment strategies.[3] While resistance levels and epidemiologic trends vary significantly by region, comparative insights from low-burden settings—such as those in Japan—can inform preventive efforts in higher-prevalence regions.[4]

Species of the genus *Acinetobacter* are non-fermentative, Gram-negative rods that occur widely in the environment, including in the soil and the human intestinal tract.[5] Among clinical isolates, *A. baumannii* predominates; it is regarded as the most clinically significant species because it readily acquires multidrug resistance and is prone to cause outbreaks.[1] Although *Acinetobacter* spp. exhibit low pathogenicity in healthy individuals, they are well-known opportunistic pathogens in hosts with impaired immune defenses.[6] Due to its a formidable capacity to accumulate diverse resistance mechanisms, *A. baumannii* was placed in the WHO's 2024 list of priority pathogens; specifically, MDR *A. baumannii*

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was categorized into the highest "Critical" group, together with third-generation cephalosporin-resistant *Enterobacterales* that produce extended-spectrum β-lactamases (ESBLs) and rifampicin-resistant *Mycobacterium tuberculosis*.[3]

Japan occupies a somewhat distinctive position in East and Southeast Asia: national surveillance systems have reported comparatively low prevalence of carbapenem-resistant *A. baumannii*, even though the country is closely connected to higher-burden regions through travel and healthcare exchange. This situation provides an opportunity to examine which elements of surveillance, infection control, and antimicrobial stewardship may help maintain low levels, and which structural differences may explain why resistance has not yet risen to the levels observed elsewhere.

This article reviews the current status of and countermeasures against infections caused by MDR *Acinetobacter*, with particular emphasis on Japan's clinical and epidemiologic experience, and contrasts these findings with reports from higher-burden settings. By doing so, it seeks to bridge the gap between regional surveillance data, resistance mechanisms, and practical guidance for diagnosis, infection control, and treatment.

Definition of Multidrug Resistance

MDR *Acinetobacter* infection is designated a Category V condition under Japan's Infectious Diseases Control Law; any suspected case must be reported to public health authorities.[7] A notifiable case is defined as an infection caused by an *Acinetobacter* isolate resistant to all three of the following antimicrobial classes: broad-spectrum β-lactams (operationally, carbapenems), aminoglycosides, and fluoroquinolones.[7] Colonized but asymptomatic carriers are excluded from this reporting requirement.

Internationally, however, the term "MDR" typically refers to resistance to at least one agent in three or more antimicrobial classes, regardless of which specific classes are involved.[8] The United States (US) Center for Disease Control (CDC) and Europe CDC (ECDC) also provide guidance, and the Infectious Diseases Society of America offers specific definitions for carbapenem-resistant *A. baumannii* (CRAB), which is a clinically important subset of MDR *A. baumannii*.[9]

Since these definitions differ in stringency, caution is required when comparing MDR *Acinetobacter* surveillance data across countries. Japan's legal definition is more restrictive, which likely contributes to the low number of notifiable cases; however, this may also under-represent the burden of clinically significant resistance.[7,9] Understanding this discrepancy is essential for aligning infection control policies and interpreting global surveillance trends.[9]

Resistance Mechanisms in the Genus *Acinetobacter*

The resistance mechanisms of *Acinetobacter* spp. can be grouped into three major categories: (i) enzymatic inactivation of antimicrobials, such as hydrolysis or modification by β-lactamases;[10] (ii) reduced intracellular accumulation due to decreased outer-membrane permeability and/or upregulated efflux pumps;[11] and (iii) alteration of drug targets through genetic mutations or post-translational modifications.[12] The interplay of these mechanisms underlies the organism's MDR phenotype. A summary table of resistance mechanisms is presented in Table 1.

Resistance to β-Lactam Antimicrobials

β-Lactamase Production

β-Lactamases hydrolyze β-lactam antibiotics and are classified into four Ambler classes (A–D). *Acinetobacter* spp. produce enzymes in all four classes.[16] Class A enzymes include narrow-spectrum β-lactamases and ESBLs such as $bla_{\text{TEM-92}}$, bla_{SHV}, and $bla_{\text{GES-11}}$.[13] Cefotaximase, Munich (CTX-M)-type ESBLs are rarely detected in *A. baumannii* in Japan; however, *Klebsiella pneumoniae* carbapenemase (KPC)-type carbapenemases have been reported overseas.[14,15] Class B enzymes (metallo-β-lactamases, MBLs) include imipenemase, New Delhi MBL, Verona integron-encoded MBL, and Seoul imipenemase, which hydrolyze nearly all β-lactams except monobactams.[17] Class C enzymes include the intrinsic *Acinetobacter*-derived cephalosporinase (ADC). Expression is upregulated by *ISAba1* insertion upstream of the *adc* gene, conferring resistance.[18,19] Variants such as ADC-57 and ADC-68 can even hydrolyze carbapenems.[20,21] Clinically, class D enzymes are the most important; these include oxacillin-hydrolyzing β-lactamase (OXA)-type carbapenemases such as OXA-23, −24/40, −58, −143, and −235.[22,23] Chromosomal OXA-51-like enzymes also

Table 1 Resistance Mechanisms in *Acinetobacter baumannii*: Determinants, Genetic Context, and Phenotypic Impact

Major Class/Mechanism	Representative Determinants	Typical Genetic Context/ Regulatory Element	Expected Phenotypic Impact	Notes/Clinical Relevance
β-lactams—β-lactamases (Ambler A)	TEM, SHV, GES (eg, blaTEM-92, blaSHV, blaGES-11);[13] CTX-M (rare in A. baumannii in Japan);[14] KPC reported overseas[15]	Plasmid or chromosome; ESBL-associated promoters[13–16]	Reduced activity of penicillins/ cephalosporins (ESBL); potential reduced carbapenem activity (KPC)	CTX-M uncommon in A. baumannii in Japan;[14] KPC mostly outside Japan[15]
β-lactams — β-lactamases (Ambler B, MBLs)	IMP, NDM, VIM, SIM[17]	Mobile elements; diverse contexts (monobactams spared)[17]	Reduced activity of nearly all β-lactams except monobactams	Different therapeutic implications vs OXA producers[17]
β-lactams — β-lactamases (Ambler C)	ADC (intrinsic);[18] overexpression via ISAba1 upstream;[18,19] variants ADC-57, ADC-68[20,21]	Chromosome; ISAba1 activation[18,19]	Reduced activity of broad-spectrum cephalosporins; some variants associated with higher carbapenem MICs[20,21]	Upregulated ADC commonly co-exists with other mechanisms[18,19]
β-lactams — β-lactamases (Ambler D, OXA)	OXA-23, OXA-24/40, OXA-58, OXA-143, OXA-235;[22,23] chromosomal OXA-51–like (upregulated with ISAba1)[24]	Often IS/ transposon-associated; ISAba1 provides promoter[22–24]	Reduced activity of carbapenems (class D carbapenemases)	SENTRY 2020–2021: OXA in 96.3% of CRAB; OXA-23 most frequent (73.1%)[25]
Outer-membrane proteins (porins/OMPs)	OmpA loss;[26] CarO disruption;[27,28] AbuO[29]	Chromosomal; insertion/ disruption events[26–29]	Reduced influx leading to higher MICs; CarO disruption associated with high carbapenem MICs;[27,28] AbuO contributes to efflux of ceftriaxone and meropenem[29]	Permeability changes amplify β-lactam resistance[26–29]
Efflux pumps (RND & others)	AdeABC (AdeA/AdeB/AdeC),[30] AdeIJK, AdeFGH;[31] AbeM[32]	Chromosomal; regulator mutations lead to overexpression[30–32]	Higher MICs across multiple classes; increased resistance to carbapenems/ cephalosporins and tigecycline[30–32]	AdeABC is most characterized; contributes to XDR phenotypes with other mechanisms[30,32]
PBPs (target alterations)	Loss of PBP1b; mutations in PBP3[33,34]	Chromosomal mutations[33,34]	Higher carbapenem MICs; altered β-lactam binding[33,34]	Often co-occurs with β-lactamases/efflux[33,34]
Aminoglycosides — modifying enzymes	APH, AAC, ANT families[35]	Plasmid or chromosome[35]	Reduced activity of gentamicin/amikacin and related agents[35]	Multiple enzymes can yield high-level resistance[35]
Aminoglycosides —16S rRNA methyltransferases	eg, armA[36]	Often plasmid-borne[36]	High-level resistance across aminoglycosides[36]	Frequently accompanies other mechanisms[36]
Aminoglycosides — uptake/efflux and permeability	Efflux upregulation; membrane impermeability[36]	Chromosomal[36]	Moderate-to-high resistance[36]	Synergizes with enzymatic mechanisms[35,36]
Fluoroquinolones — target mutations	gyrA/gyrB, parC/parE (QRDR mutations)[37]	Chromosomal[37]	Reduced class-wide activity (ciprofloxacin/levofloxacin/ moxifloxacin)[37]	Primary mechanism; stepwise accumulation common[37]
Fluoroquinolones — efflux	AdeABC, AdeIJK, AdeFGH[31,38]	Chromosomal; regulator mutations[31,38]	Further MIC increases[31,38]	Acts additively with QRDR mutations[31,38]

Notes: Superscript numbers indicate the reference numbers of the literature summarized in this table.
Abbreviations: ESBL, extended-spectrum β-lactamase; MBL, metallo-β-lactamase; QRDR, quinolone resistance–determining region; CRAB, carbapenem-resistant A. baumannii; MIC, minimum inhibitory concentration.

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contribute to resistance when *ISAba1* is inserted upstream.[24] Notably, in a SENTRY surveillance study (2020–2021), 96.3% of CRAB isolates produced an OXA enzyme, most frequently OXA-23 (73.1%).[25]

Outer-Membrane Proteins (Omps)

Loss or alteration of outer-membrane proteins can reduce drug influx as follows: (i) OmpA loss reduces cephalosporin susceptibility;[26] (ii) CarO is critical for carbapenem entry, and disruption leads to high carbapenem minimum inhibitory concentrations (MICs);[27,28] and (iii) AbuO contributes to the efflux of ceftriaxone and meropenem.[29]

Efflux Pumps

Of the efflux pumps, the AdeABC pump is the best-characterized: AdeB mediates drug extrusion, AdeA acts as a membrane fusion protein, and AdeC forms an outer-membrane channel.[30] Overexpression contributes to resistance against carbapenems and cephalosporins. AdeIJK and AbeM also confer resistance to imipenem.[32]

Penicillin Binding Protein (PBP) Alterations

PBP mutations—including the loss of PBP1b and mutations in PBP3—have been linked to increased carbapenem MICs.[33,34]

Mechanisms of Resistance to Aminoglycosides

A. baumannii develops aminoglycoside resistance through: (i) aminoglycoside-modifying enzymes such as aminoglycoside phosphotransferases, aminoglycoside acetyltransferases, and aminoglycoside adenylyltransferase;[35] (ii) 16S ribosomal ribonucleic acid methyltransferases that alter ribosomal targets; and (iii) reduced uptake via efflux or membrane impermeability.[36] Aminoglycoside resistance is observed in approximately 19–31% of clinical isolates.[39]

Mechanisms of Resistance to Fluoroquinolones

Fluoroquinolones inhibit deoxyribonucleic acid gyrase and topoisomerase IV. Mutations in quinolone resistance-determining regions of *gyrA, gyrB, parC*, and *parE* are the main resistance mechanism.[37] Overexpression of efflux pumps in the resistance-nodulation-division family (eg, AdeABC, AdeIJK, and AdeFGH) further elevates resistance.[31,38]

Genomic Epidemiology, Plasmid Dynamics, and Mobile Elements (β-Lactams /Aminoglycosides/Fluoroquinolones)

Building on the classical mechanisms outlined above, recent genomics shows that A. baumannii strengthens resistance mainly by acquiring and rearranging mobile genetic elements—especially plasmids, insertion sequences, and transposons—which determine where key genes sit and how strongly they are expressed.[40] For β-lactams, plasmids are the principal vehicles for carbapenemases, most often OXA-23–family enzymes, which are frequently embedded in compact cassettes that move between plasmid and chromosome on transposons such as Tn2006.[41] Occasionally, metallo-β-lactamases like NDM-1 are acquired on Tn125, yielding broad β-lactam resistance in diverse genomic contexts.[42] Expression can be amplified when the insertion sequence ISAba1 lands upstream of the intrinsic cephalosporinase (blaADC) or chromosomal OXA-51-like gene, supplying a strong promoter that pushes borderline MICs into the resistant range.[43] Many *Acinetobacter* plasmids are built from replication backbones that accept short pdif modules flanked by XerC/XerD sites, enabling rapid capture, reshuffling, and excision of resistance cassettes without altering the core genome.[44] For aminoglycosides, high-level resistance commonly follows acquisition of the 16S rRNA methyltransferase armA, which has repeatedly emerged and spread in clinical settings via plasmids.[45] For fluoroquinolones, target-site mutations and efflux upregulation remain the primary drivers, but mobile elements modulate impact by changing promoter context or copy number of accessory determinants, thereby nudging phenotypes from borderline to resistant in conjunction with those core mechanisms.[28] Taken together, across β-lactams, aminoglycosides, and fluoroquinolones, resistance phenotypes are shaped by an interaction between mechanism and genomic context: identical enzymes or target alterations can produce divergent susceptibility profiles according to their genomic location (plasmid versus chromosome), promoter environment (eg, activation by ISAba1), and gene dosage (eg, module duplication or cointegrate formation).

Epidemiology of MDR *Acinetobacter*: Global and Japan

Owing to its environmental hardiness and ability to survive on minimal nutrients, MDR *Acinetobacter* has become a globally significant healthcare pathogen.[46] Resistance rates, however, vary markedly by region.

The SENTRY Antimicrobial Surveillance Program (2013–2016) showed that susceptibility to meropenem—a key carbapenem—was lowest in Latin America (13.7%), followed by the Asia-Pacific region (21.0%), Europe (22.2%), and the US (54.9%).[47] More recent data from 2020–2021 show similar trends, particularly in regions with limited antimicrobial stewardship infrastructure or high baseline antibiotic consumption.[25]

In contrast, Japan remains a notable outlier, with consistently high carbapenem susceptibility among *Acinetobacter* isolates. According to the Japan Nosocomial Infections Surveillance program, 98.3% of clinical isolates remained susceptible to meropenem in 2023.[48]

The reasons for Japan's favorable resistance profile are not fully understood. It may reflect a combination of factors—including relatively prudent antimicrobial use, structured national surveillance, and differences in healthcare infrastructure; however, definitive causal links remain unclear.[48,49] Importantly, the consistently low prevalence of CRAB in Japan provides a unique context for proactive preparedness and may offer indirect insights for regions currently experiencing rising resistance.[48,49] Comparative analysis of microbiological practices, reporting systems, and treatment approaches across countries could help elucidate effective elements of containment.[49]

Infection Control Measures in Healthcare Facilities

Globally, infection prevention and control (IPC) measures for MDR *Acinetobacter* share core principles, with frameworks from the CDC, ECDC, and WHO emphasizing standard precautions, contact isolation, environmental decontamination, and antimicrobial stewardship.[50] Japan's national IPC strategies are broadly aligned with these principles, although implementation details—such as frequency of screening or cleaning protocols—may vary by institution and resource availability.[51] The rarity of MDR *Acinetobacter* in Japan presents both a challenge and an opportunity: healthcare personnel may have limited familiarity with containment protocols, yet even single cases can trigger rapid escalation due to the perceived outbreak potential.[52]

Standard Infrastructure

Hospitals must rigorously enforce standard precautions, antimicrobial stewardship, and environmental hygiene. Infection control teams should: (i) audit hand hygiene product consumption and compliance, (ii) monitor antimicrobial use and provide feedback to prescribers, (iii) perform regular environmental safety rounds, and (iv) arrange periodic external audits to validate local infection control practices.[53]

Environmental Reservoirs

Common bacteria can survive for months on dry surfaces, and patients' surroundings are often contaminated with their own flora.[54] As emphasized by the CDC and ECDC guidelines, scheduled surface cleaning and immediate removal of visible soil are essential components of infection control.[50,54] *A. baumannii* has been detected on bed rails up to nine days after patient discharge and on other surfaces for up to five months,[55] underscoring the importance of environmental hygiene in MDR *Acinetobacter* containment. High-risk items include ventilators, urine collection systems, sinks, mattresses, pillows, curtains, washcloths, toys, and cleaning tools; in addition, ventilator circuits and nebulizers have been implicated in several outbreaks.[56]

Even floors or walls—though unlikely direct sources of transmission—should be thoroughly decontaminated once contamination is suspected or confirmed. Routine "screening cultures" are rarely cost-effective and should be limited to patients with a history of MDR *Acinetobacter* colonization, recent overseas hospital care, or direct transfer from facilities experiencing active outbreaks.[57] Japan has reported several instances of MDR *Acinetobacter* imported from overseas hospitals, particularly among patients transferred after long-term treatment abroad.[58] Although such events are rare, they highlight the importance of preemptive screening and isolation for patients with recent international healthcare exposure—a strategy consistent with global best practices.[50,57]

Response to a Carrier or Outbreak

Since MDR *Acinetobacter* is still extremely rare in Japan, every carrier demands heightened precautions, including the following: (i) immediate single-room isolation with full contact precautions; (ii) dedicated, non-shared medical equipment; and (iii) rapid and clear communication within the healthcare facility.[51,52]

If multiple carriers are identified, nosocomial transmission should be presumed and the response should be escalated accordingly, following these steps: (i) establish an outbreak response team and conduct regular incident briefings; (ii) disinfect high-touch surfaces daily with appropriate agents; (iii) perform targeted environmental cultures to verify the effectiveness of cleaning protocols; and (iv) if containment efforts fail, temporarily halt new admissions and seek external expert consultation (eg, from tertiary care infection control units).[52]

Eradication of MDR *Acinetobacter* from colonized patients is typically difficult and slow, and institutional outbreaks can spread rapidly if not managed decisively.[59] Therefore, timely detection and firm control responses remain critical.

For global readers, Japan's experience underscores a valuable but often overlooked aspect of MDR pathogen control: early containment during the low-incidence phase. While high-burden countries struggle with endemic spread, Japan's current situation demonstrates the importance of swift action, rigorous isolation, and environmental vigilance, even when case numbers are low. Institutions in other low-prevalence settings may benefit from similar preparedness approaches before CRAB becomes entrenched.

Treatment of MDR *Acinetobacter* Infections

In most hospitals worldwide, *Acinetobacter* infections predominantly present as healthcare-associated infections, such as catheter-related bloodstream infections or ventilator-associated pneumonia.[60] Community-onset fulminant *Acinetobacter* pneumonia has been well-documented in parts of Southeast Asia and northern Australia, but remains rare in Japan and many high-income countries.[61]

Managing infections caused by MDR *A. baumannii* is particularly challenging due to limited therapeutic options and frequent host comorbidities.[62] Determining whether the isolate reflects colonization or true infection is often difficult, especially in respiratory specimens. Moreover, MDR *Acinetobacter* isolates frequently exhibit resistance to multiple drug classes, leaving clinicians with few effective choices.[63]

Despite international research efforts, no universal standard regimen has been established for CRAB. The 2024 Infectious Diseases Society of America (IDSA) guidelines emphasize that treatment decisions should be individualized based on the infection site, severity, available agents, and local susceptibility patterns.[64] The mechanisms of action, representative clinical evidence, and principal limitations of the major antimicrobial agents used in the management of MDR *A. baumannii* and CRAB infections are summarized in Table 2.

Table 2 Mechanisms, Clinical Evidence, and Key Limitations of Antimicrobial Agents Used Against Multidrug-Resistant and Carbapenem-Resistant *Acinetobacter baumannii*

Agent[a]	Mechanism/Activity	Use/Evidence	Key Limitations/ Adverse Events
Sulbactam/ durlobactam[57–59]	β-lactam/β-lactamase inhibitor combination; randomized trials show promising results.	Used for CRAB, often with imipenem/cilastatin; RCT evidence supports its efficacy.	—
High-dose sulbactam[57,60]	Intrinsic bactericidal activity against *A. baumannii* via penicillin-binding proteins.	Bactericidal effect requires ~9 g/day of **pure** sulbactam; rarely implemented due to logistical difficulty.	Practical challenges in achieving the required high dose.
Colistin[57,61,62]	Polymyxin with activity against MDR *A. baumannii*; efficacy decreases when MIC >2 μg/mL.	2024 IDSA discourages monotherapy (poor lung penetration and higher mortality in randomized trials); typically combined with ≥1 active agent.	Nephrotoxicity is a major concern.

(*Continued*)

Table 2 (Continued).

Agent[a]	Mechanism/Activity	Use/Evidence	Key Limitations/ Adverse Events
Tigecycline[57,63]	Active against MDR Gram-negative organisms, including *A. baumannii*; activity wanes when the MIC is >1 μg/mL.	Monotherapy is associated with higher mortality in some studies; combination therapy is often preferred.	Gastrointestinal adverse effects (eg, nausea), which are dose-dependent.
Cefiderocol[57,64,65]	Siderophore cephalosporin; dual uptake via passive diffusion and active iron transport may confer advantages in some phenotypes.	Increasingly used (often in combination) for severe MDR *A. baumannii*; the clinical data is heterogeneous—monotherapy should be approached cautiously.	Variability in evidence exists; there is a potential for phenotype-dependent efficacy.

Notes: [a]Superscript numbers indicate the reference numbers of the literature summarized in this table.
Abbreviations: CRAB, carbapenem-resistant *A. baumannii*; IDSA, Infectious Diseases Society of America; MDR, multidrug-resistant; MIC, minimum inhibitory concentration; RCT, randomized controlled trial.

Sulbactam/Durlobactam

Sulbactam/durlobactam, a β-lactam/β-lactamase inhibitor combination approved by the US FDA in 2023, has shown promising results in randomized controlled trials.[65] Although the agent is not yet available in Japan, it has been increasingly adopted for CRAB infections in the US and parts of Europe, often in combination with imipenem/cilastatin.[65] Its absence in Japan highlights the need for alternative strategies in regions where access is limited.[66]

High-Dose Sulbactam

In Japan, sulbactam is commonly administered as ampicillin/sulbactam for enzyme inhibition. However, sulbactam itself possesses intrinsic bactericidal activity against *A. baumannii* by targeting PBPs.[67] Achieving this effect requires high doses—9 g of pure sulbactam per day—which may be logistically difficult; therefore, this is rarely implemented in current Japanese practice.

Colistin

Colistin remains available as a salvage therapy for MDR *Acinetobacter* in Japan and other countries.[68] Its efficacy decreases when the MIC exceeds 2 μg/mL, and nephrotoxicity is a major concern.[69] The 2024 IDSA guidelines discourage monotherapy due to suboptimal lung penetration and increased mortality observed in randomized trials.[64] Therefore, colistin is typically used in combination with at least one other active agent.

Tigecyclin

Tigecycline is licensed in Japan and internationally for use against various MDR Gram-negative organisms, including *A. baumannii*.[64] However, its activity diminishes when the MIC exceeds 1 μg/mL,[64] and some studies link monotherapy with higher mortality rates than combination therapy.[70] Gastrointestinal side effects, particularly nausea, are common and dose-dependent.[64]

Cefiderocol

Cefiderocol, a siderophore cephalosporin developed in Japan, has gained global attention for its broad-spectrum activity against carbapenem-resistant Gram-negative bacilli, including *A. baumannii*.[71] It is now approved in North America, Europe, and Asia, and is increasingly used as part of combination therapy in severe MDR *Acinetobacter* infections. Its dual-uptake pathway via passive diffusion and active iron transport may offer advantages in certain resistance phenotypes.[71] Nevertheless, clinical data remain heterogeneous, and cefiderocol monotherapy should be approached cautiously.[72]

Should Antimicrobials Be Combined?

The IDSA guidelines recommend combination therapy for CRAB infections.[64] This is based on three considerations: (i) limited external validity of trial data, (ii) lack of robust clinical evidence for monotherapy (except for sulbactam/durlobactam), and (iii) frequent delays in initiating active therapy due to initial empirical treatment failure.[64,65] Given the high mortality associated with CRAB, using two active agents may increase the likelihood of therapeutic success.[64]

Globally, the management of CRAB remains a moving target. Regional variations in drug availability, susceptibility patterns, and antimicrobial policy complicate the development of standardized algorithms.[63,66] In all settings, combination therapy guided by in vitro activity and clinical judgment remains the mainstay of treatment, pending broader access to newer agents such as sulbactam/durlobactam and future comparative efficacy data.[65,66]

Emerging and Investigational Therapeutics for *A. baumannii*

Two investigational approaches with peer-reviewed evidence merit brief inclusion.

First, zosurabalpin, a first-in-class inhibitor that blocks lipopolysaccharide (LPS) transport in *Acinetobacter*, has shown potent activity against carbapenem-resistant *A. baumannii* in vitro and in animal models, with mechanism and resistance pathways characterized in complementary studies in 2024. These reports establish on-target action at the LptB_2FGC transporter and demonstrate efficacy signals in preclinical infection models.[73]

Second, the synthetic lipopeptide QPX9003 (also reported as BRII-693) represents a redesigned polymyxin-class agent with reduced toxicity liabilities. Preclinical work confirmed activity against MDR *A. baumannii*, and a peer-reviewed Phase 1 study has reported acceptable safety, pharmacokinetics, and exposures compatible with preclinical PK/PD targets, supporting progression to patient studies.[74]

In addition, bacteriophage therapy has accumulating peer-reviewed clinical literature in *A. baumannii*, including case-based applications (eg, inhaled or personalized phage) and reviews summarizing feasibility and safety considerations. While standardization and regulatory pathways remain evolving, these reports illustrate a viable adjunct in selected multidrug-resistant cases.[75]

Conclusions

Multidrug-resistant *Acinetobacter baumannii* remains difficult to treat and control in hospitals. Its broad drug resistance, delays in recognizing the organism, and the growing number of vulnerable patients all contribute to poor outcomes. These problems are common across many regions.

Japan is a useful comparison because current prevalence is relatively low. The main lesson is not that Japan offers a universal model, but that early and steady effort—good surveillance, basic infection-prevention practices, and careful antibiotic use—can help keep rates from rising. Seeing how these policies work in a low-burden setting gives other regions practical ideas they can adapt to their own systems.

Looking ahead, three needs are clear. First, patients should have fair access to new drugs, and treatment should reflect the local resistance mechanisms. Second, faster tests that hint at the underlying mechanism would help clinicians choose therapy sooner and better. Third, countries should share data and coordinate infection control and antibiotic stewardship to limit the spread of high-risk clones across borders. In short, MDR *Acinetobacter* is both an urgent threat and a preventable path: by learning from low-burden settings and acting early, health systems can avoid future surges.

Abbreviations

CDC, Center for Disease Control; CRAB, Carbapenem-resistant *Acinetobacter baumannii*; ECDC, European Center for Disease Control; ESBL, Extended-spectrum β-lactamase; IDSA, Infectious Diseases Society of America; IPC, Infection prevention and control; MBL, Metallo-β-lactamase; MDR, Multidrug-resistant; MIC, Minimum inhibitory concentration; US, United States; WHO, World Health Organization.

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