

[ORIGINAL ARTICLE]

OPEN ACCESS

Healthcare-Associated Infections Caused by Multidrug-Resistant Organisms: Risk Factors, Clinical Outcomes, and Prevention Strategies

Sonia Afroz¹; Rafique Us Saleheen²; Mohammed Fahad³; Maliha Sahreen Hossain⁴; Sayema Afroz Eva⁵; Kazi Foyeza Akther⁶

¹Department of Microbiology, National Institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh

²Directorate General of Health Services (DGHS), Bangladesh

³Department of Biology, The City College of New York, City University of New York, New York, USA

⁴Shaheed Tajuddin Ahmad Medical College, Gazipur, Bangladesh

⁵North South University, Dhaka, Bangladesh

⁶Consultant, Obstetrics and Gynaecology, BRB Hospitals Limited, Dhaka, Bangladesh

Corresponding Author: Sonia Afroz | soniaafrozdr@gmail.com

Abstract

Background: Multidrug-resistant organisms (MDROs) complicate healthcare-associated infections (HAIs), yet the relationships among antecedent exposures, initial antimicrobial activity, patient outcomes, and prevention-related exposures require careful interpretation among patients already infected. We compared MDR and non-MDR HAIs across eight hospitals in New York, USA.

Methods: This multicentre observational cohort study analysed 650 adults with culture-confirmed HAIs occurring more than 48 hours after admission across eight anonymised hospitals in New York, USA, between January 2024 and June 2024. The primary endpoint was MDR status at the index infection; secondary endpoints included active empirical therapy, septic shock, post-HAI hospital stay, in-hospital death and 30-day all-cause death. Logistic regression models adjusted for clinical covariates and hospital and infection-site indicators; negative-binomial regression assessed post-HAI stay. Associations are presented with 95% confidence intervals (CIs).

Results: Among 650 patients, 193 (29.7%) had MDR HAIs. MDR status was associated with prior antibiotic exposure (adjusted odds ratio [aOR] 2.44, 95% CI 1.64–3.63), documented MDRO colonisation (aOR 4.87, 2.98–7.96), previous hospitalisation (aOR 1.60, 1.10–2.35), and an early central line (aOR 1.76, 1.14–2.73). An admission prevention-bundle indicator was inversely associated with MDR status (aOR 0.45, 0.31–0.66). Active initial therapy occurred in 51.8% of MDR versus 87.1% of non-MDR cases. MDR HAIs were associated with septic shock (aOR 1.68, 1.04–2.72) and longer post-HAI stay (adjusted incidence-rate ratio 1.37, 1.24–1.50), but not 30-day mortality (aOR 1.06, 0.60–1.85).

Conclusions: Among patients already experiencing HAIs, antecedent antibiotic use and MDRO carriage identified important resistance-associated profiles, while MDR cases experienced substantial treatment mismatch and morbidity. Prevention-bundle associations are noncausal, and mortality differences remained uncertain. Multicentre validation and intervention studies are warranted.

Keywords: healthcare-associated infection; antimicrobial resistance; multidrug-resistant organisms; empirical antimicrobial therapy; septic shock; infection prevention; multicentre cohort

Received: 18 April 2025

Revised: 25 April 2025

Accepted: 13 May 2025

Published: 15 June 2025

Cite this article

Afroz S, Saleheen RU, Fahad M, Hossain MS, Eva SA, Akther KF. Healthcare-Associated Infections Caused by Multidrug-Resistant Organisms: Risk Factors, Clinical Outcomes, and Prevention Strategies. J Evid-Based Med Res. 2025.

© The Author(s). Formatting proof for editorial review. Publication metadata subject to journal confirmation. CC BY 4.0 licence applies upon publication by the journal.

1. Introduction

Healthcare-associated infections remain a formidable challenge to safe inpatient care. Even in settings with mature surveillance systems, bloodstream infections, pneumonia, urinary tract infections and surgical-site infections generate preventable complications, consume hospital resources and expose vulnerable patients to prolonged antimicrobial treatment. Changes in HAI prevalence observed across US hospitals have demonstrated that improvement is achievable, although the problem has not disappeared [1]. In low-resource health systems, the burden may be even greater because constrained laboratory capacity, overcrowding and uneven infection-prevention implementation intersect with more limited treatment options [2]. Global intensive-care data further emphasise the clinical severity and geographic heterogeneity of infection-related outcomes [3].

Antimicrobial resistance adds a second layer of risk. Analyses of global and regional burden indicate that bacterial resistance contributes substantially to preventable mortality and disability, and projections suggest a continuing challenge over coming decades [4–6]. Observational cohorts of resistant bloodstream infection have also documented excess hospital stay and adverse outcomes, while highlighting how results depend on pathogen selection, clinical case mix and the comparator used [7]. Resistance emerges within an ecological system shaped by antimicrobial exposure, patient movement, infection-control practices and transmission opportunities [8,9]. International priority-setting has therefore focused particularly on resistant Gram-negative pathogens and selected Gram-positive organisms encountered in hospitals [10].

Clinically, the question is not merely which isolates are resistant. It is whether resistant infections can be anticipated using information available before infection, whether their empirical treatment is less likely to be active, and which complications remain associated with MDR status after accounting for patient severity. A further question concerns admission prevention bundles: these may indicate stronger infection-control practice, yet observational comparisons among patients who all develop HAI cannot establish whether an intervention prevents infection in the source hospital population. Failure to distinguish infection incidence from resistance distribution among infected patients can lead to exaggerated conclusions.

We evaluated a multicentre cohort of patients with healthcare-associated infections in New York, USA, to characterise the distribution of MDR pathogens, identify factors associated with resistance, examine the appropriateness of initial antimicrobial treatment and compare infection-related morbidity and mortality with non-MDR cases. We additionally examined the relationship between an admission prevention-bundle indicator and resistance status, recognising that associations observed among infected patients cannot be interpreted as estimates of preventive efficacy.

2. Methods

2.1 Study design, setting and population

This multicentre observational cohort study included patients treated between January 2024 and June 2024 at eight anonymised hospitals in New York, USA. The participating institutions comprised teaching hospitals, tertiary-care centres and general hospitals, identified as H01–H08. The cohort consisted of 650 unique adult patients aged 18–89 years with culture-confirmed HAIs occurring more than 48 hours after hospital admission; observed infection onset was on hospital day 4 or later. Each patient contributed one index HAI episode and was classified as having an MDR or non-MDR infection. All 650 cohort records were included in the complete-case analyses. The study focused on resistance among patients with HAI rather than the incidence of HAI among all admitted patients. Reporting follows relevant STROBE recommendations for observational research [29].

2.2 Outcome and resistance definitions

The primary classification was multidrug-resistant (MDR) versus non-MDR HAI for the index culture-confirmed infection. Recorded resistance categories included extended-spectrum beta-lactamase (ESBL) production, carbapenem resistance, other MDR phenotypes, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE) and carbapenem-resistant *Acinetobacter baumannii*. These categories were analysed using their clinical record classifications, without imposing retrospectively reconstructed susceptibility criteria [11]. Infection syndromes were classified as bloodstream infection, pneumonia, urinary tract infection or surgical-site infection. Comparisons of specific resistance categories are descriptive and refer to the index organism.

2.3 Microbiological and infection ascertainment

Index HAIs were identified by the recorded occurrence of a healthcare-associated infection more than 48 hours after admission together with a positive clinical culture. For each episode, the index organism, documented resistance phenotype and susceptibility-based activity of empirical antimicrobial therapy were used to classify resistance and initial treatment concordance. Clinical data were linked to the index infection episode for the assessment of subsequent complications and outcomes. Laboratory phenotype categories were compared as recorded across hospitals; no uniform institutional susceptibility-testing method was assumed.

2.4 Patient characteristics and clinical exposures

Covariates comprised age, sex, Charlson Comorbidity Index excluding age points, receipt of antibiotics and hospitalisation within the preceding 90 days, documented MDRO colonisation at admission, immunosuppression, and central venous catheter, mechanical ventilation or urinary catheter exposure within the first 48 hours of admission. An admission prevention-bundle indicator was analysed as a recorded binary exposure rather than a randomised intervention. Intensive-care-unit (ICU) status and Sequential Organ Failure Assessment (SOFA) score were recorded at the index infection assessment. Because ICU status and organ dysfunction may coincide with or follow infection onset, analyses incorporating these factors were regarded as severity-adjusted associations. The Charlson and SOFA instruments have established clinical applications [30,31].

2.5 Clinical endpoints and follow-up

Active empirical antimicrobial therapy was defined as an initial treatment regimen with activity against the index isolate. Time to effective therapy was the interval, in hours, between infection onset and the first active regimen; this value was zero for initially active regimens. Time to active therapy was also summarised separately among patients whose empirical regimen was inactive. Further outcomes were septic shock during the HAI episode, number of hospital days following infection until discharge or inpatient death, total hospital length of stay, in-hospital death and all-cause death within 30 days of infection onset. The 30-day mortality endpoint was assessed for all 650 patients, and inpatient deaths were included within the 30-day mortality count.

2.6 Statistical analysis

All 650 patients were retained, with complete values for the variables used in the analyses. Descriptive data are reported as frequencies and percentages for categorical variables and medians and interquartile ranges (IQRs) for continuous variables. Between-group contrasts used Pearson chi-square tests for categorical measures and Mann-Whitney U tests for non-normally distributed continuous variables. A Wilson confidence interval was calculated for the proportion of MDR infections. All statistical tests were two-sided, and inferential findings were interpreted alongside effect sizes, confidence intervals and the observational study design rather than solely according to statistical significance.

2.7 Regression modelling

The primary MDR-status model included age (per 10 years), sex, Charlson score, antecedent antibiotics and hospitalisation, known colonisation, immunosuppression, early central line, ventilation, urinary catheter, admission bundle, ICU-at-index, SOFA-at-index, infection-site indicators and hospital fixed effects. Covariates were selected for clinical relevance and ascertainment availability, not stepwise statistical significance. Binomial generalised linear models with a logit link yielded adjusted odds ratios (aORs); heteroskedasticity-consistent HC3 standard errors furnished 95% CIs. Hospital fixed effects accommodated baseline differences in resistance distribution across the eight sites. We did not rely on asymptotic cluster-robust standard errors with only eight hospital clusters. A sensitivity model omitted concurrently measured ICU/SOFA variables and infection-site adjustment to focus on antecedent correlates.

For septic shock, effective initial therapy, in-hospital death and 30-day death, separate logistic models estimated the association of MDR status while adjusting for age, sex, Charlson score, index ICU and SOFA, infection site and hospital. Because index severity might lie on a pathway between resistant infection and subsequent outcomes, models excluding ICU/SOFA served as sensitivity analyses. Initial treatment activity was not included as a covariate in the main MDR-outcome models, as it could mediate resistance-

associated harm. Post-HAI hospital days were analysed by negative-binomial regression with the same clinical case-mix and hospital terms; the adjusted incidence-rate ratio (IRR) describes a relative mean stay, not a causal length-of-stay effect. In-hospital death can truncate length of stay and was not treated as independent censoring. Regression analyses were performed in Python using statsmodels and scipy. No imputation was required.

2.8 Ethical considerations

Ethical approval for the study was obtained from the participating hospitals, and informed consent was obtained from enrolled patients. Patient information was pseudonymised for analysis, and participating institutions were identified only by study codes to maintain hospital confidentiality.

2.9 Population denominator and interpretation

The primary descriptive measure was the proportion of MDR infections among the 650 culture-confirmed HAI episodes. This measure is distinct from the incidence of HAIs among hospital admissions or hospital patient-days. The MDR proportion may reflect the combined distribution of susceptible and resistant infections within the infected population and cannot alone quantify hospital-wide transmission or resistance acquisition. The organism- and syndrome-specific analyses used their respective observed HAI denominators. Associations involving the admission prevention bundle were therefore interpreted in relation to MDR classification among HAI cases, not as reductions in HAI risk for the overall hospital population.

3. Results

3.1 Cohort composition and case mix

The analysis included 650 patients with HAI from eight anonymised New York hospitals (Figure 1). The cohort comprised 193 MDR HAIs (29.7%; 95% Wilson CI 26.3%–33.3%) and 457 non-MDR HAIs (70.3%). Patients with MDR infection were older (median 58 versus 52 years), had greater comorbidity and organ dysfunction at index assessment, and more often had recent antibiotic exposure (43.5% versus 26.5%), previous hospitalisation (46.6% versus 37.9%), documented MDRO colonisation (28.0% versus 9.2%) and a central line during the first 48 hours (40.4% versus 29.8%). An admission prevention-bundle indicator was present in 42.0% of MDR versus 58.9% of non-MDR cases. Baseline clinical characteristics and exposures are presented in Table 1.

3.2 Pathogen and infection-site distribution

Of the 650 infections, 216 were pneumonias (33.2%), 155 bloodstream infections (23.8%), 143 urinary tract infections (22.0%) and 136 surgical-site infections (20.9%). Species representation included *E. coli* (139), *P. aeruginosa* (135), *K. pneumoniae* (132), *A. baumannii* (85), *S. aureus* (83) and *E. faecium* (76). MDR percentages varied modestly by species, from 27.4% in *P. aeruginosa* to 32.9% in *A. baumannii*; no species was categorically classified as resistant. Among 193 MDR isolates, the coded phenotypes were other MDR (46), carbapenem-resistant (44), ESBL-producing (29), carbapenem-resistant *A. baumannii* (28), MRSA (25) and VRE (21). These descriptive phenotype labels are mutually exclusive as supplied, not a reconstructed taxonomy (Table 2; Figure 2).

Correlates of MDR infection. In the multivariable model, antecedent antibiotic exposure (aOR 2.44, 95% CI 1.64–3.63), previous hospitalisation (1.60, 1.10–2.35), documented colonisation (4.87, 2.98–7.96), immunosuppression (1.71, 1.02–2.86) and a central line in the first 48 hours (1.76, 1.14–2.73) were associated with MDR status. The admission bundle was inversely associated (0.45, 0.31–0.66). After covariate control, age, sex, Charlson score, index ICU status, index SOFA, ventilation and urinary catheter use had CIs

including the null. Hospital-level differences persisted after adjustment, but estimates for individual hospital indicators should not be construed as rankings of infection-prevention quality. Excluding concurrent severity and infection-site terms in the sensitivity analysis produced similar associations for antibiotic exposure (aOR 2.44), colonisation (4.87), central-line exposure (1.65) and admission bundle (0.45) (Table 3; Figure 3).

3.3 Empirical antimicrobial activity and complications

Initial therapy was active in 100/193 MDR cases (51.8%) versus 398/457 non-MDR cases (87.1%), a difference of –35.3 percentage points. The adjusted odds of active empirical treatment in MDR infection were 0.16 (95% CI 0.10–0.24). Among 152 patients whose first regimen was inactive, the time to effective therapy was 39.4 hours (IQR 29.2–51.3) for MDR infections and 20.6 hours (17.1–26.9) for non-MDR infections. Septic shock was recorded in 41 MDR cases (21.2%) and 57 non-MDR cases (12.5%); the adjusted association remained detectable (aOR 1.68, 1.04–2.72). Post-HAI stay was longer for MDR infections (median 15 versus 10 days), with an adjusted mean-stay ratio of 1.37 (1.24–1.50) (Tables 4–5; Figure 4).

3.4 Mortality

In-hospital deaths occurred in 20/193 (10.4%) MDR cases versus 35/457 (7.7%) non-MDR cases, and death by day 30 in 23/193 (11.9%) versus 44/457 (9.6%). Neither mortality comparison remained statistically distinguishable after case-mix adjustment: the aORs were 1.12 (95% CI 0.61–2.07) for in-hospital death and 1.06 (0.60–1.85) for 30-day death. Excluding index ICU and SOFA did not materially alter the inference for 30-day mortality (aOR 1.16, 0.66–2.03). These CIs allow clinically relevant harm and do not establish equivalence.

4. Discussion

In this eight-hospital cohort of patients with confirmed HAIs in New York, approximately three in ten infections were classified as multidrug resistant. The most distinctive patient characteristic was documented MDRO carriage on admission, which was associated with almost fivefold higher adjusted odds of an MDR index infection. Recent antibiotic exposure and hospitalisation were also associated with resistance, supporting the clinical value of eliciting prior healthcare contact and antimicrobial history at the point of empirical treatment selection. The findings align with the ecological understanding that antibiotic selection pressure and healthcare exposure shape resistant pathogen distribution [8,9], but the associations should not be presented as proof of biological causation within this nonrandomised cohort.

The observation that known colonisation was particularly informative has immediate practical relevance. A recorded resistant organism may signal elevated probability of resistant subsequent infection; nevertheless, colonisation should not be treated as a mandate for unrestricted broad-spectrum therapy. The balance depends on infection syndrome, organism-specific historical susceptibilities, acute severity and local antibiograms. Prior investigations have connected ESBL infection with delayed effective treatment [12], while classic critical-care studies raised concern about initial inactivity in severe infection [13]. In our data, activity of the initial empirical regimen differed by 35 percentage points between MDR and non-MDR cases, and patients requiring a subsequent active agent experienced notably longer delays. The observed disparity provides a rationale for locally tailored empiric pathways, prompt diagnostic review and early de-escalation when susceptibilities become available.

Timely active therapy remains crucial in severe infection, although the literature does not support indiscriminate broad-spectrum escalation. Studies of severe sepsis and septic shock have linked

delays in effective antibiotics to adverse outcomes, while acknowledging confounding within observational analyses [14–16,35]. A meta-analysis also supports the clinical importance of appropriate empirical coverage [17]. The observed disparity in initial activity in this cohort illustrates how resistance complicates antimicrobial selection. However, time to first active therapy and initial coverage are closely linked because initially active regimens have an interval of zero by definition. Thus, associations between MDR status, empirical treatment activity and clinical outcomes should not be conflated with a causal estimate of the effect of delayed therapy. Treatment selection also depends on infection focus, source control, physiological instability and clinical judgement.

After severity and case-mix adjustment, MDR infection remained associated with septic shock and prolonged hospitalisation, yet the mortality estimates were imprecise and included the null. This pattern is clinically plausible: resistance may complicate treatment and recovery without producing an easily measurable independent death signal in a sample with 67 thirty-day deaths. The absence of a statistically significant mortality association must not be rewritten as evidence that resistance is harmless. Studies of resistant bloodstream infections have reported context-dependent mortality and length-of-stay consequences [6,7]; comparing those estimates with our mixed-site HAI cohort requires attention to eligibility, infection severity, pathogen mix and endpoint definitions. Death also shortens observed inpatient follow-up, so a regression of stay duration cannot fully capture the illness burden that would occur under an alternative clinical outcome.

The inverse association between the recorded admission prevention-bundle indicator and MDR status deserves cautious consideration. Although the adjusted aOR of 0.45 suggests an association within this HAI cohort, it does not estimate the effectiveness of a prevention programme in reducing incident HAI across hospital admissions. Exposure to prevention measures may vary by hospital, baseline infection risk and clinical practice; the association could therefore be influenced by residual confounding, selection effects and confounding by indication. Furthermore, the composite bundle indicator does not isolate the contribution of a particular practice. This result is best considered hypothesis-generating and consistent with the need to evaluate specific preventive interventions using designs that establish exposure, adherence and outcomes independently.

Evidence from intervention research supports multimodal infection prevention, although programme effectiveness depends on context. Central-line safety bundles have reduced catheter-associated bloodstream infections, and practice guidance emphasises insertion technique, device maintenance and daily necessity review [20,23]. Intensive-care decolonisation and enhanced terminal disinfection have shown benefits under defined conditions, while studies of gloves, gowns and selective decontamination highlight the importance of local implementation and resistance ecology [21,22,32,33]. Current guidance further addresses prevention of hospital-acquired pneumonia, catheter-associated urinary tract infection, surgical-site infection and MRSA transmission [24–28]. These external findings strengthen the rationale for coordinated infection prevention but should not be used to assign causal effectiveness to the recorded bundle indicator in this cohort.

Several integrated priorities emerge. First, admission screening and communication systems should make prior organism history available when a new HAI is suspected, especially for patients recently exposed to antibiotics or hospital care. Second, empirical protocols should account for syndrome-specific resistance patterns and the probability of severe illness, followed by microbiology-guided optimisation rather than automatic indefinite broad-

spectrum treatment. Stewardship programmes have reduced resistant-organism and *Clostridioides difficile* outcomes across multiple settings and have improved important prescribing targets [18,19]. Rapid molecular diagnostics, when combined with stewardship, may shorten delays to effective therapy in bloodstream infections [36]. Third, programmes should ensure appropriate indication and early removal of invasive devices, reinforce hand hygiene and transmission precautions, and audit bundle completion using process as well as outcome measures. The current observational findings motivate these efforts, but their actual effects require intervention-level surveillance.

Study strengths include assessment of four major HAI syndromes, complete observations for recorded 30-day outcomes, participation of eight institutions representing different levels of hospital care, and consistent examination of antecedent exposures, empirical treatment and subsequent morbidity. Hospital indicators helped account for differences in resistance distribution across institutions, and sensitivity analyses explored the influence of adjustment for concurrent illness severity. Crucially, the analysis distinguished the prevalence of MDR classification among patients already infected from the incidence of HAI among all hospitalised patients, reducing the risk of denominator-related misinterpretation.

Several limitations warrant consideration. The cohort was restricted to culture-confirmed HAIs and therefore cannot establish the population-wide incidence of HAI, the risk of acquiring resistance during admission or infection-attributable mortality. Resistance phenotypes were analysed using recorded classifications rather than reconstructed isolate-level susceptibility profiles. The prevention-bundle indicator is an observational composite measure and does not estimate the causal effect of any individual prevention practice. Eight hospitals offer within-region diversity but do not necessarily represent all New York healthcare institutions. In addition, ICU admission and SOFA scores at the infection assessment may be consequences of infection; conditioning on these variables can affect interpretation of severity-adjusted estimates. Antimicrobial treatment decisions, unmeasured patient factors, competing risks of discharge and death, and indication-related differences in prevention practice may contribute residual confounding. The associations with septic shock, length of stay and bundle status should consequently be interpreted as observational rather than intervention effects. Consistent clinical surveillance definitions and transparent outcome ascertainment remain essential in multisite studies [34].

Future work should prospectively enumerate all at-risk admissions and patient-days, link admission colonisation to strain-level microbiology and time-varying device exposure, and document bundle delivery with auditable fidelity measures. Such a design could estimate HAI incidence separately from resistance prevalence among cases. Explicit preinfection severity, detailed antibiotic timing, microbiological testing standards, and multistate methods for discharge and death would support less biased outcome attribution. Cluster-randomised or rigorously controlled interrupted time-series evaluations may then test the effects of prevention and stewardship strategies rather than simply identify their correlates.

The clinical utility of any resistance-risk profile must also be judged against harms from unnecessary antimicrobial breadth. A patient with colonisation or previous antibiotic exposure may have increased odds of MDR infection, yet many such patients in the present cohort experienced susceptible HAIs. A bedside algorithm that automatically classifies all exposed patients as requiring reserve agents could therefore increase selection pressure without proportional benefit. Future predictive work should evaluate calibration, discrimination, decision thresholds, local resistance prevalence and net clinical benefit rather than simply report significant risk-factor coefficients. Risk stratification is most

defensible when it narrows the group needing immediate broad coverage, incorporates the severity of the current syndrome, and triggers timely reassessment once cultures identify the actual pathogen. This approach is consistent with the broader aim of maintaining initial adequacy while conserving antimicrobial effectiveness over time.

5. Conclusions

Multidrug-resistant organisms accounted for 29.7% of 650 culture-confirmed HAIs in an eight-hospital cohort. Prior antibiotic use, hospitalisation, documented resistant-organism colonisation, immunosuppression and early central-line exposure were associated with MDR status, whereas a recorded admission bundle was inversely associated. MDR cases were substantially less likely to receive initially active treatment and experienced more septic shock and longer postinfection stays. Thirty-day and in-hospital mortality associations remained uncertain after adjustment. Effective responses should integrate admission risk information, prompt laboratory-supported therapy, antimicrobial stewardship and independently evaluated prevention programmes without inferring causality from infected-only observational comparisons.

Declarations

Ethics approval and informed consent: Ethical approval was obtained at all eight participating hospitals, and informed consent was obtained from enrolled patients.

Funding: The study received no external or institutional funding.

Conflicts of interest: The authors declare no conflicts of interest.

Data availability: Individual-level patient data are confidential and are not publicly available.

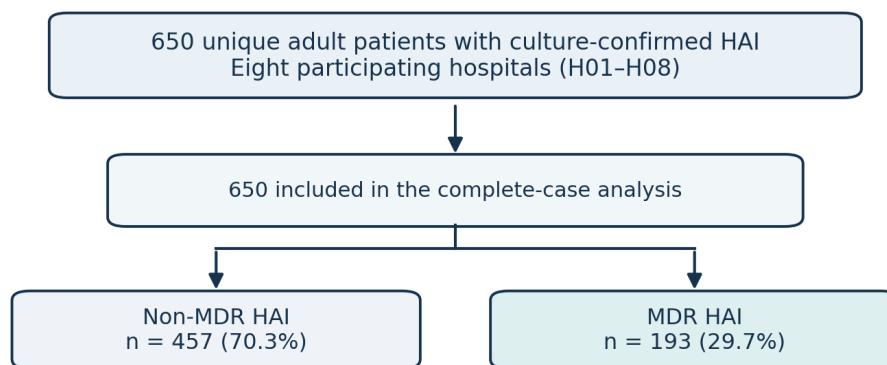
References

- Magill SS, O'Leary E, Janelle SJ, et al. Changes in prevalence of health care-associated infections in U.S. hospitals. *N Engl J Med*. 2018;379:1732–1744. doi:10.1056/NEJMoa1801550.
- Allegranzi B, Bagheri Nejad S, Combescure C, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. *Lancet*. 2011;377:228–241. doi:10.1016/S0140-6736(10)61458-4.
- Vincent JL, Sakr Y, Singer M, et al. Prevalence and outcomes of infection among patients in intensive care units in 2017. *JAMA*. 2020;323:1478–1487. doi:10.1001/jama.2020.2717.
- Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022;399:629–655. doi:10.1016/S0140-6736(21)02724-0.
- GBD 2021 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050. *Lancet*. 2024;404:1199–1226. doi:10.1016/S0140-6736(24)01867-1.
- Cassini A, Högberg LD, Plachouras D, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and European Economic Area in 2015. *Lancet Infect Dis*. 2019;19:56–66. doi:10.1016/S1473-3099(18)30605-4.
- de Kraker MEA, Davey PG, Grundmann H. Mortality and hospital stay associated with resistant *Staphylococcus aureus* and *Escherichia coli* bacteremia: estimating the burden of antibiotic resistance in Europe. *PLoS Med*. 2011;8:e1001104. doi:10.1371/journal.pmed.1001104.
- Holmes AH, Moore LSP, Sundsfjord A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet*. 2016;387:176–187. doi:10.1016/S0140-6736(15)00473-0.
- Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance—the need for global solutions. *Lancet Infect Dis*. 2013;13:1057–1098. doi:10.1016/S1473-3099(13)70318-9.
- Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect Dis*. 2018;18:318–327. doi:10.1016/S1473-3099(17)30753-3.
- Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect*. 2012;18:268–281. doi:10.1111/j.1469-0691.2011.03570.x.
- Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum beta-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2007;60:913–920. doi:10.1093/jac/dkm318.
- Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest*. 1999;115:462–474. doi:10.1378/chest.115.2.462.
- Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34:1589–1596. doi:10.1097/01.CCM.0000217961.75225.E9.
- Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med*. 2014;42:1749–1755. doi:10.1097/CCM.0000000000000330.
- Seymour CW, Gesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. *N Engl J Med*. 2017;376:2235–2244. doi:10.1056/NEJMoa1703058.
- Paul M, Shani V, Muchtar E, Kariv G, Robenshtok E, Leibovici L. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. *Antimicrob Agents Chemother*. 2010;54:4851–4863. doi:10.1128/AAC.00627-10.
- Schuts EC, Hulscher MEJL, Mouton JW, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. *Lancet Infect Dis*. 2016;16:847–856. doi:10.1016/S1473-3099(16)00065-7.
- Baur D, Gladstone BP, Burkert F, et al. Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and *Clostridium difficile* infection: a systematic review and meta-analysis. *Lancet Infect Dis*. 2017;17:990–1001. doi:10.1016/S1473-3099(17)30325-0.
- Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med*. 2006;355:2725–2732. doi:10.1056/NEJMoa061115.
- Huang SS, Septimus E, Kleinman K, et al. Targeted versus universal decolonization to prevent ICU infection. *N Engl J Med*. 2013;368:2255–2265. doi:10.1056/NEJMoa1207290.
- Anderson DJ, Chen LF, Weber DJ, et al. Enhanced terminal room disinfection and acquisition and infection caused by multidrug-resistant organisms and *Clostridium difficile* (the Benefits of Enhanced Terminal Room Disinfection study): a cluster-randomised, multicentre, crossover study. *Lancet*. 2017;389:805–814. doi:10.1016/S0140-6736(16)31588-4.
- Buetti N, Marschall J, Drees M, et al. Strategies to prevent central line-associated bloodstream infections in acute-care hospitals: 2022 update. *Infect Control Hosp Epidemiol*. 2022;43:553–569. doi:10.1017/ice.2022.87.
- Klompas M, Branson R, Cawcutt K, et al. Strategies to prevent ventilator-associated pneumonia, ventilator-associated events, and nonventilator hospital-acquired pneumonia in acute-care hospitals: 2022 update. *Infect Control Hosp Epidemiol*. 2022;43:687–713. doi:10.1017/ice.2022.88.
- Patel PK, Advani SD, Kofman AD, et al. Strategies to prevent catheter-associated urinary tract infections in acute-care hospitals: 2022 update. *Infect Control Hosp Epidemiol*. 2023;44:1209–1231. doi:10.1017/ice.2023.137.
- Calderwood MS, Anderson DJ, Bratzler DW, et al. Strategies to prevent surgical site infections in acute-care hospitals: 2022 update. *Infect Control Hosp Epidemiol*. 2023;44:695–720. doi:10.1017/ice.2023.67.
- Popovich KJ, Aureden K, Ham DC, et al. SHEA/IDSA/APIC practice recommendation: strategies to prevent methicillin-resistant *Staphylococcus aureus* transmission and infection in acute-care hospitals: 2022 update. *Infect Control Hosp Epidemiol*. 2023;44:1039–1067. doi:10.1017/ice.2023.102.
- Yokoe DS, Advani SD, Anderson DJ, et al. Executive summary: a compendium of strategies to prevent healthcare-associated infections in acute-care hospitals: 2022 updates. *Infect Control Hosp Epidemiol*. 2023;44:1540–1554. doi:10.1017/ice.2023.138.

29. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med.* 2007;4:e296. doi:10.1371/journal.pmed.0040296.
30. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40:373–383. doi:10.1016/0021-9681(87)90171-8.
31. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med.* 1996;22:707–710. doi:10.1007/BF01709751.
32. Harris AD, Pineles L, Belton B, et al. Universal glove and gown use and acquisition of antibiotic-resistant bacteria in the ICU: a randomized trial. *JAMA.* 2013;310:1571–1580. doi:10.1001/jama.2013.277815.
33. de Smet AMGA, Kluytmans JAJW, Cooper BS, et al. Decontamination of the digestive tract and oropharynx in ICU patients. *N Engl J Med.* 2009;360:20–31. doi:10.1056/NEJMoa0800394.
34. Rhee C, Dantes R, Epstein L, et al. Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009–2014. *JAMA.* 2017;318:1241–1249. doi:10.1001/jama.2017.13836.
35. Liu VX, Fielding-Singh V, Greene JD, et al. The timing of early antibiotics and hospital mortality in sepsis. *Am J Respir Crit Care Med.* 2017;196:856–863. doi:10.1164/rccm.201609-1848OC.
36. Timbrook TT, Morton JB, McConeghy KW, Caffrey AR, Mylonakis E, LaPlante KL. The effect of molecular rapid diagnostic testing on clinical outcomes in bloodstream infections: a systematic review and meta-analysis. *Clin Infect Dis.* 2017;64:15–23. doi:10.1093/cid/ciw649.

Figures

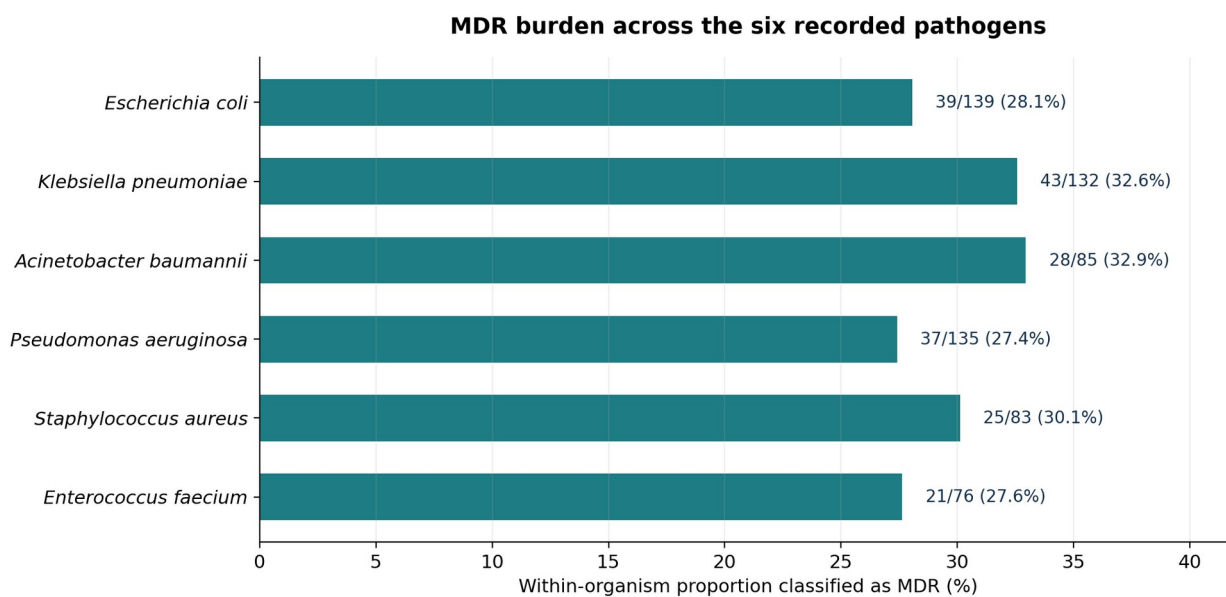
Figure 1. Cohort definition and resistance-status distribution.



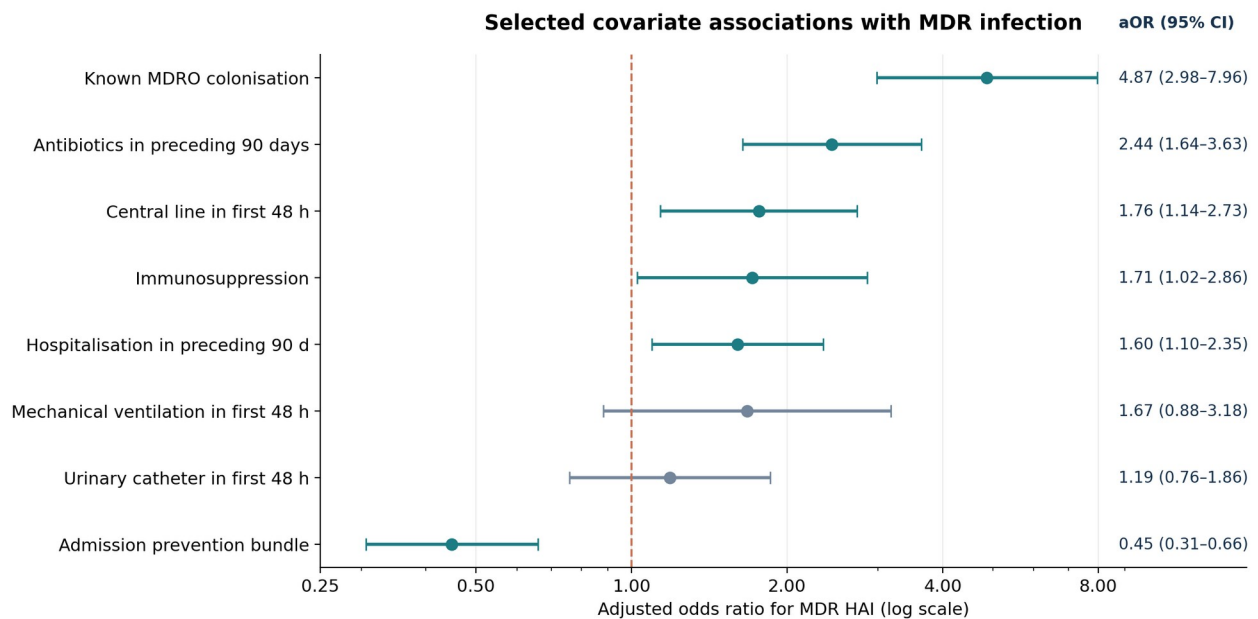
Classification at index healthcare-associated infection

Each patient contributed one index culture-confirmed HAI episode and was classified by MDR status (n=650).

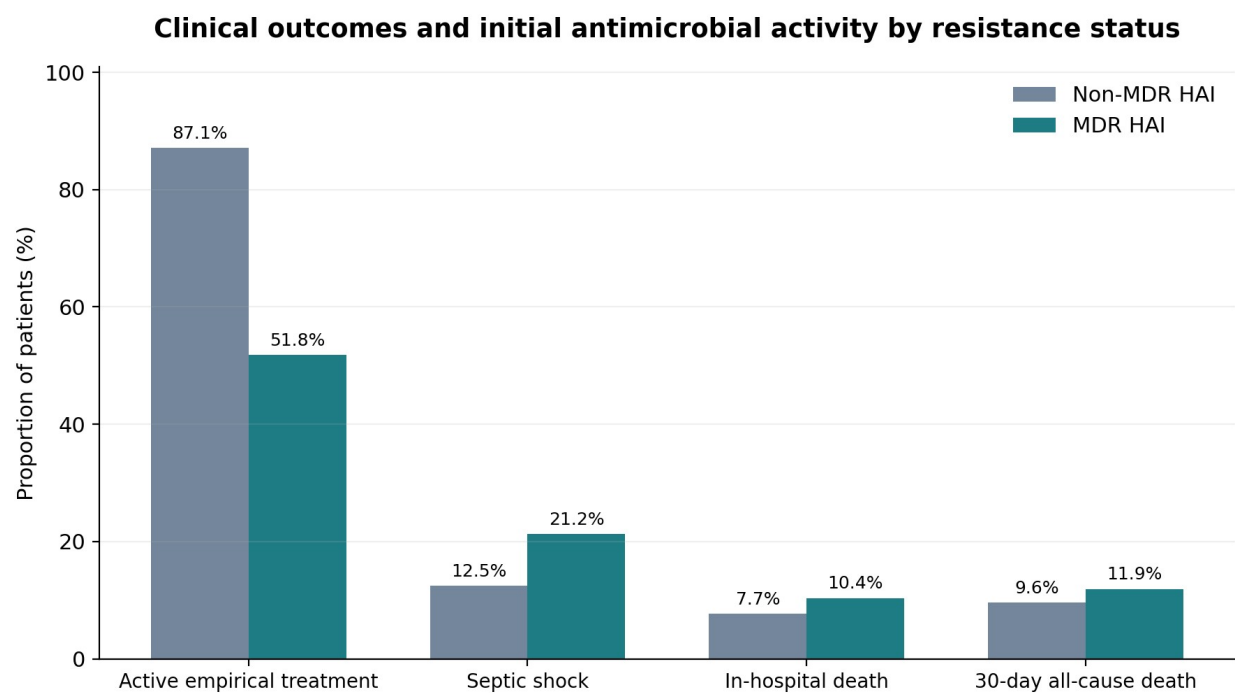
Figure 2. Organism-specific MDR proportions.



Each proportion represents MDR cases divided by all cases with that organism. Values are descriptive, not incidence estimates; no hypothesis of organism-level differences was prespecified.

Figure 3. Selected patient-level correlates of MDR HAI.

Dots and horizontal bars depict adjusted odds ratios and 95% confidence intervals from the full multivariable model. Dashed vertical line indicates the null (OR=1). Hospital and site indicators are included in the model but not plotted.

Figure 4. Empirical treatment activity and complications by MDR status.

Unadjusted group percentages for initial active therapy, septic shock, in-hospital death and 30-day all-cause death. Adjusted associations are reported in Table 5; the mortality contrasts are not statistically distinguishable.

Tables

Table 1. Baseline characteristics and pre-/peri-infection exposures by MDR status

Characteristic	Overall (N=650)	Non-MDR (n=457)	MDR (n=193)
Age, years; median (IQR)	54.0 (37.0–73.0)	52.0 (36.0–72.0)	58.0 (42.0–75.0)
Male sex	340 (52.3)	233 (51.0)	107 (55.4)
Charlson Comorbidity Index; median (IQR)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	1.0 (0.0–2.0)
ICU at index assessment	162 (24.9)	106 (23.2)	56 (29.0)
SOFA score at index; median (IQR)	3.0 (1.0–5.0)	3.0 (1.0–5.0)	4.0 (2.0–6.0)
Antibiotic exposure, previous 90 days	205 (31.5)	121 (26.5)	84 (43.5)
Hospitalisation, previous 90 days	263 (40.5)	173 (37.9)	90 (46.6)
Known MDRO colonisation at admission	96 (14.8)	42 (9.2)	54 (28.0)
Immunosuppression at admission	98 (15.1)	62 (13.6)	36 (18.7)
Central line, first 48 admission hours	214 (32.9)	136 (29.8)	78 (40.4)
Mechanical ventilation, first 48 hours	137 (21.1)	88 (19.3)	49 (25.4)
Urinary catheter, first 48 hours	210 (32.3)	146 (31.9)	64 (33.2)
Enhanced prevention bundle at admission	350 (53.8)	269 (58.9)	81 (42.0)
HAI onset, admission day; median (IQR)	9.0 (7.0–10.0)	9.0 (7.0–10.0)	9.0 (7.0–11.0)

Data are n (%) unless otherwise stated. Charlson Index excludes age points. SOFA and ICU status refer to the index infection assessment.

Table 2. Anatomical syndromes, organisms, and recorded resistance phenotypes

Characteristic	Overall n (%)	Non-MDR n (%)	MDR n (%)	MDR within type
Bloodstream	155 (23.8)	102 (22.3)	53 (27.5)	34.2%
Pneumonia	216 (33.2)	152 (33.3)	64 (33.2)	29.6%
Urinary tract	143 (22.0)	106 (23.2)	37 (19.2)	25.9%
Surgical site	136 (20.9)	97 (21.2)	39 (20.2)	28.7%
ORGANISMS				
Escherichia coli	139 (21.4)	100 (21.9)	39 (20.2)	28.1%
Klebsiella pneumoniae	132 (20.3)	89 (19.5)	43 (22.3)	32.6%
Acinetobacter baumannii	85 (13.1)	57 (12.5)	28 (14.5)	32.9%
Pseudomonas aeruginosa	135 (20.8)	98 (21.4)	37 (19.2)	27.4%
Staphylococcus aureus	83 (12.8)	58 (12.7)	25 (13.0)	30.1%

Characteristic	Overall n (%)	Non-MDR n (%)	MDR n (%)	MDR within type
Enterococcus faecium	76 (11.7)	55 (12.0)	21 (10.9)	27.6%
RESISTANCE PHENOTYPE (MDR ONLY)				
ESBL-producing	29	—	29 (15.0)	—
Carbapenem-resistant	44	—	44 (22.8)	—
Other MDR	46	—	46 (23.8)	—
MRSA	25	—	25 (13.0)	—
VRE	21	—	21 (10.9)	—
Carbapenem-resistant A. baumannii	28	—	28 (14.5)	—

Organism and site categories each sum to 650. Recorded resistance categories sum to 193 MDR infections. Percentages are calculated using group denominators unless otherwise stated.

Table 3. Multivariable associations with multidrug resistance among HAI cases

Covariate	Adjusted OR (95% CI)	P value
Age, per 10 years	1.07 (0.96–1.18)	0.222
Male sex	1.30 (0.89–1.90)	0.167
Charlson index, per point	1.17 (0.98–1.40)	0.091
ICU at index	0.81 (0.38–1.70)	0.577
SOFA at index, per point	1.03 (0.93–1.13)	0.561
Antibiotics in previous 90 days	2.44 (1.64–3.63)	<0.001
Hospitalisation in previous 90 days	1.60 (1.10–2.35)	0.015
Known MDRO colonisation	4.87 (2.98–7.96)	<0.001
Immunosuppression	1.71 (1.02–2.86)	0.040
Central line in first 48 hours	1.76 (1.14–2.73)	0.011
Ventilation in first 48 hours	1.67 (0.88–3.18)	0.114
Urinary catheter in first 48 hours	1.19 (0.76–1.86)	0.453
Enhanced admission prevention bundle	0.45 (0.31–0.66)	<0.001

Binomial generalised linear model with HC3 robust standard errors (N=650). In addition to listed terms, the model includes hospital and infection-site fixed effects; those nuisance coefficients are omitted for clarity. Index acuity is concurrent with infection and should not be interpreted as temporally antecedent. OR, odds ratio.

Table 4. Antimicrobial activity, complications, and utilisation outcomes

Outcome	Non-MDR (n=457)	MDR (n=193)	Absolute difference
Initial regimen active against isolate	398 (87.1)	100 (51.8)	-35.3 pp
Septic shock during HAI	57 (12.5)	41 (21.2)	+8.8 pp
In-hospital death	35 (7.7)	20 (10.4)	+2.7 pp
All-cause death within 30 days	44 (9.6)	23 (11.9)	+2.3 pp
Time to active treatment, all patients (hours)	0.0 (0.0–0.0)	0.0 (0.0–38.6)	—
Time to active treatment if initial regimen inactive (hours)	20.6 (17.1–26.9)	39.4 (29.2–51.3)	—
Post-HAI stay, days	10.0 (7.0–15.0)	15.0 (10.0–21.0)	—
Total inpatient stay, days	20.0 (16.0–25.0)	24.0 (18.0–31.0)	—

Outcomes are n (%) or median (IQR); pp, percentage points. Effective empirical therapy denotes activity of the initial treatment against the index organism. Treatment-delay summaries among patients requiring an alternative active regimen use n=59 non-MDR and n=93 MDR. Time to active therapy is zero for initially active regimens. Continuous outcomes are descriptive; causal effects are not inferred.

Table 5. Case-mix-adjusted associations of MDR HAI with clinical outcomes

Outcome	Model	MDR versus non-MDR	P value
Initial empirical regimen active	Adjusted odds ratio	0.16 (0.10–0.24)	<0.001
Septic shock	Adjusted odds ratio	1.68 (1.04–2.72)	0.036
In-hospital death	Adjusted odds ratio	1.12 (0.61–2.07)	0.706
30-day all-cause death	Adjusted odds ratio	1.06 (0.60–1.85)	0.847
Post-HAI inpatient days	Adjusted mean-stay ratio (NB)	1.37 (1.24–1.50)	<0.001

Individual models adjusted for age per decade, sex, Charlson index, ICU and SOFA at index, infection-site categories and hospital fixed effects. HC3 standard errors were used. NB, negative-binomial regression. The incidence-rate ratio represents a relative mean stay; inpatient death may truncate follow-up. These are associations, not causal effects.