

Archives of Medical Microbiology

Review Article

Clinical Outcomes of antimicrobial stewardship programs in Patients with biofilm-associated infection

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Received: 25 February 2026; Accepted: 19 May 2026; Published: 25 August 2026.

Citation of this article: Nair P, Bose D, Patel K (2026) Clinical Outcomes of antimicrobial stewardship programs in Patients with biofilm-associated infection. Arch Med Microbiol, 8(1): 01-06. DOI: [10.5281/zenodo.22812873](https://doi.org/10.5281/zenodo.22812873)

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Abstract

Background: Biofilm-associated infection, involving prosthetic joints, vascular catheters, and cardiac devices, routinely resists antibiotic regimens that succeed against the same organism growing planktonically, raising the question of whether generic antimicrobial stewardship programs serve this population as well as they serve infections without a biofilm component.

Objective: This review synthesizes the clinical outcomes literature on antimicrobial stewardship programs applied to patients with biofilm-associated infection, examining whether standard stewardship metrics track meaningful outcomes here and whether biofilm-specific protocol adaptation improves cure and reinfection rates.

Methods: We synthesized peer-reviewed clinical outcomes studies, systematic reviews and meta-analyses of stewardship program effectiveness, and society guideline documents for biofilm-associated device and implant infection.

Findings: General stewardship programs reliably reduce antimicrobial consumption, resistant-organism incidence, and *C. difficile* infection, but the smaller literature stratified by clinical outcome shows a weaker signal, and mature device-infection guidelines instead rely on prolonged, biofilm-active, often combination therapy with source control, a pattern at odds with duration- and de-escalation-focused stewardship defaults.

Conclusions: Extending stewardship's demonstrated benefits to biofilm-associated infection requires pathway-specific protocols audited on guideline concordance rather than generic targets, supported by laboratory infrastructure able to flag biofilm-relevant clinical context.

Keywords: antimicrobial stewardship; biofilm; device-associated infection; antibiotic resistance; prosthetic joint infection

1. Introduction

Biofilm-associated infection is now recognized as a distinct clinical problem rather than a variant presentation of ordinary planktonic bacterial disease. A biofilm is a structured community of microorganisms embedded in a self-produced extracellular matrix that adheres to a living or inert surface, and its formation on prosthetic joints, vascular catheters, cardiac devices, endotracheal tubes, and damaged native tissue accounts for a large share of the infections that fail first-line antimicrobial therapy [1,2]. Within this matrix, bacteria adopt a phenotype that tolerates antibiotic concentrations many times higher than those that kill the same organism growing planktonically, through mechanisms that include reduced metabolic activity, matrix-limited drug penetration, altered gene expression, and the persistence of a small dormant subpopulation that survives even bactericidal exposure [3,4,5]. Device-associated and implant-associated infections illustrate the clinical stakes: prosthetic joint infection, catheter-related bloodstream infection, and cardiac-device infection each carry a biofilm component that routinely defeats standard-duration antibiotic courses and often mandates device removal for cure [6,7,8].

Antimicrobial stewardship programs were built to address a different but overlapping problem: the overuse and misuse of antibiotics that drives resistance, adverse events, and cost, largely in infections without a biofilm component [9,10]. Core stewardship activities, prospective audit with feedback, prior-authorization restriction, de-escalation guidance, dose optimization, and duration limits, were validated primarily in pneumonia, urinary tract infection, and bloodstream infection cohorts, where a defined course of active antibiotic reliably clears the pathogen once susceptibility is confirmed [11,12]. Whether the same stewardship logic, and in particular its emphasis on shortening therapy and de-escalating to narrower agents once cultures return, serves patients whose infection is biofilm-associated is a

genuinely open clinical question, because the pharmacodynamic assumptions that justify shorter, narrower courses in planktonic infection do not hold inside a biofilm [13,14].

This review synthesizes the clinical outcomes literature bearing on antimicrobial stewardship programs applied to patients with biofilm-associated infection, asking three linked questions: whether generic stewardship metrics (days of therapy, de-escalation rate, guideline concordance) track meaningful outcomes in this population; whether biofilm-specific adaptations to stewardship protocols, longer minimum durations, mandatory source control triggers, and biofilm-active regimen selection, are associated with better cure and reinfection rates than unmodified stewardship pathways; and what the surveillance and laboratory-support literature implies for building a stewardship program that serves both goals at once.

2. Methods

We synthesized peer-reviewed clinical outcomes studies, systematic reviews and meta-analyses, and society guideline documents addressing antimicrobial stewardship interventions, biofilm microbiology and antibiotic tolerance, and device- and implant-associated infection management. Sources were identified through the core stewardship guideline literature [9,10,15], systematic reviews quantifying stewardship program effect on clinical and microbiological endpoints [11,12,16,17], and the biofilm and device-infection literature describing the mechanistic basis for antibiotic tolerance and the specific management pathways used for prosthetic joint, catheter, and cardiac-device infection [2,18,6,19,20]. We prioritized studies reporting extractable clinical outcomes, cure rate, relapse or reinfection rate, treatment duration, or mortality, over studies reporting only process metrics, and we included laboratory and diagnostic-support literature relevant to how a stewardship program should be structured when

biofilm-associated infection is common in its case-mix [21,22]. Because this is a narrative synthesis rather than a formal systematic review, no quantitative pooling of heterogeneous outcome definitions was attempted; instead, findings are organized thematically around the questions in the Introduction.

3. Results

General stewardship outcomes provide the baseline against which biofilm-specific adaptation must be judged

Across hospital settings, antimicrobial stewardship programs are consistently associated with reduced antimicrobial consumption, reduced incidence of resistant-organism colonization and infection, and reduced *Clostridioides difficile* infection, with meta-analytic estimates showing roughly a 30-50% relative reduction in resistant-organism outcomes in intervention hospitals compared with controls [16]. A parallel meta-analysis of stewardship program effect on clinical and economic outcomes found consistent reductions in antimicrobial expenditure, length of stay, and, in several but not all included studies, mortality, although the mortality signal was inconsistent across study designs and settings [17]. Cochrane-level evidence for inpatient prescribing interventions similarly shows that stewardship reduces time to guideline-concordant therapy and antimicrobial duration without increasing mortality in the general inpatient population studied, though the majority of included trials enrolled patients with respiratory, urinary, or bloodstream infections rather than device- or implant-associated disease [11]. A systematic review restricted to studies reporting clinical (rather than only process) outcomes found that the strength of evidence for improved clinical outcomes, as opposed to improved prescribing metrics, was substantially weaker, and that few included studies stratified results by infection source [12]. This gap, that most stewardship outcomes evidence is drawn from infection types with a straightforward antibiotic-only cure

model, is the starting point for evaluating whether the same programs perform as well when biofilm-associated infection is embedded in the case-mix.

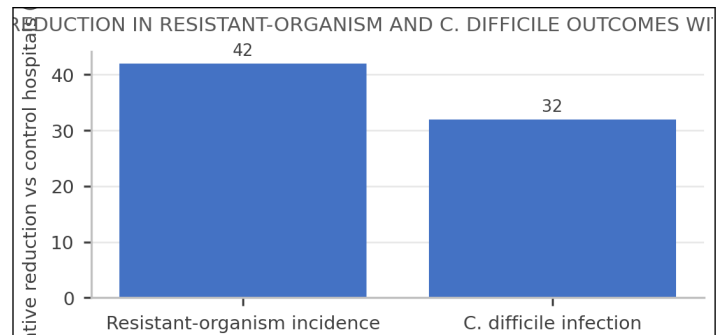


Figure 1: Meta-analytic relative reduction in resistant-organism incidence and *Clostridioides difficile* infection associated with hospital antimicrobial stewardship programs compared with control hospitals [16,17].

Biofilm microbiology explains why unmodified stewardship metrics can misfire in this population

The biofilm phenotype confers antibiotic tolerance through several convergent mechanisms: the matrix itself restricts diffusion and can inactivate certain agents before they reach embedded organisms, biofilm bacteria downregulate the metabolic pathways that many antibiotics depend on for lethality, and a persister subpopulation survives high-concentration exposure regardless of nominal susceptibility on planktonic testing [4,5,23]. Because standard clinical microbiology susceptibility testing is performed on planktonic cultures, an organism reported as susceptible can behave as clinically refractory once established in a biofilm, a discordance well documented for *Staphylococcus aureus* and *Pseudomonas aeruginosa* device infections and one that generic susceptibility-driven de-escalation protocols do not account for [21,24]. Fitzpatrick and colleagues demonstrated that biofilm-forming capacity varies substantially even within genotypically similar methicillin-resistant *S. aureus* isolates, meaning biofilm risk is not reliably predictable from organism identification and resistance phenotype alone, a further limitation for stewardship algorithms built around

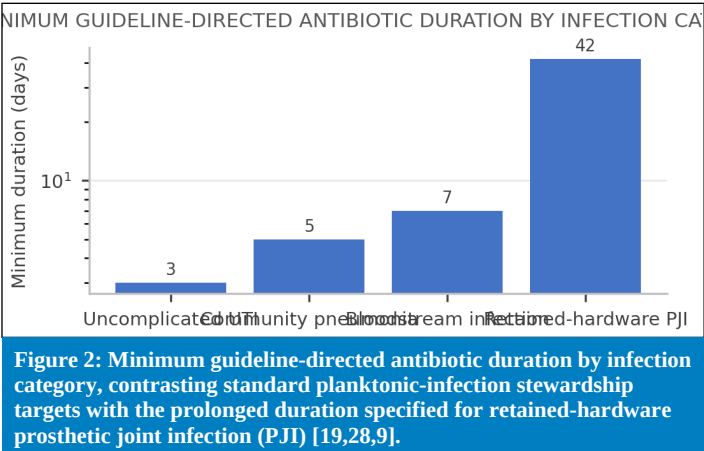
organism and susceptibility data [25]. Singh and colleagues' quorum-sensing work in chronic *Pseudomonas* lung infection illustrated the same point from a different angle: biofilm bacteria exist in physiological states, quiescent, signaling-active, dispersing, that shift over the treatment course and are invisible to a single culture-and-sensitivity result taken at diagnosis [26]. These mechanistic findings support the clinical observation that source control (device removal, debridement, drainage) rather than antibiotic selection alone is frequently the decisive determinant of cure in biofilm-associated infection [18,27].

Table 1: Mechanisms of biofilm-associated antibiotic tolerance and their implication for generic stewardship metrics [4,5,23,21].		
Mechanism	Effect on antibiotic activity	Stewardship implication
Matrix diffusion barrier	Delays or reduces effective drug concentration at target	Susceptibility breakpoint may not predict in vivo response
Reduced metabolic activity	Many bactericidal agents lose lethality against dormant cells	Shorter, planktonic-derived durations undertreat
Persister subpopulation	Survives high-concentration exposure independent of resistance genotype	De-escalation on susceptibility alone can miss relapse risk
Phenotypic heterogeneity over time	Biofilm state shifts across treatment course	Single culture-and-sensitivity result becomes outdated

Device-specific management pathways already embed biofilm-adapted stewardship principles

The clinical guideline literature for the three infection types with the most mature biofilm-associated evidence base, prosthetic joint infection, catheter-related bloodstream infection, and cardiac-device infection, converges on a pattern that departs from generic stewardship defaults: prolonged treatment durations of six weeks or more for retained-hardware prosthetic joint infection, mandatory catheter or device removal for most organisms rather than antibiotic-only salvage, and biofilm-active agents (notably rifampin-containing combinations for staphylococcal implant infection) selected specifically for their activity against

surface-adherent, slow-growing bacteria rather than purely by susceptibility breakpoint [19,6,20]. Tande and Patel's synthesis of prosthetic joint infection management explicitly frames debridement-antibiotics-implant-retention success as contingent on both organism (staphylococci with attempted retention fare worse without rifampin combination therapy) and duration, reinforcing that a stewardship pathway optimized purely for shortest effective course would systematically undertreat this population [28]. Trampuz and Widmer's review of orthopedic implant infection likewise found that outcomes hinge on the combination of surgical strategy and prolonged, biofilm-active antibiotic therapy rather than antibiotic choice in isolation [8]. Because these device-specific pathways already function as de facto biofilm-adapted stewardship protocols, embedded stewardship programs that incorporate infectious-diseases consultation and pathway concordance auditing, rather than applying generic duration and de-escalation targets uniformly, are the model most consistent with the available evidence [9,15].



Laboratory and surveillance infrastructure shapes whether stewardship programs can detect biofilm-associated failure

Table 2: Core stewardship interventions and their adaptation for biofilm-associated device infection [9,31,22,19].

Stewardship intervention	Generic target	Biofilm-associated adaptation
Prospective audit and feedback	Shortest effective duration	Extend to guideline duration for retained hardware
Prior authorization / restriction	Limit broad-spectrum use	Ensure biofilm-active agents remain accessible
De-escalation on culture result	Narrow to susceptibility	Confirm source control before narrowing
Laboratory reporting	Organism ID and susceptibility only	Flag device status and biofilm-relevant context

Morency-Potvin and colleagues' review of the microbiology laboratory's role in stewardship highlighted those diagnostic capabilities, rapid organism identification, biomarker-guided duration decisions, and communication pathways between the laboratory and the stewardship team, that determine whether a program can distinguish a biofilm-associated relapse from a new infection or a treatment failure requiring source control rather than a longer antibiotic course [22]. Surveillance systems built primarily to track resistant-organism incidence and antimicrobial consumption, the core outputs used in most published stewardship effectiveness studies, generally do not capture device retention status, debridement history, or biofilm-relevant culture data, limiting how precisely those systems can attribute clinical outcome to stewardship activity in this subgroup [29,30]. Prior-authorization and preauthorization restriction programs, among the most consistently effective individual stewardship interventions for reducing broad-spectrum use and cost, carry a specific risk in biofilm-associated infection if the restricted formulary does not include the biofilm-active agents (extended rifampin courses, certain fluoroquinolone combinations) that device-infection guidelines specify, since a restriction built around general antibiogram data can inadvertently block the regimen a biofilm-associated case actually needs [31,32].

4. Discussion

The clinical outcomes evidence supports three

conclusions about antimicrobial stewardship programs applied to patients with biofilm-associated infection. First, the outcome metrics that establish stewardship's general effectiveness, reduced consumption, reduced resistant-organism incidence, reduced C. difficile infection, are real and well replicated, but they were derived overwhelmingly from infection types without a biofilm component, and the smaller literature that stratifies by clinical (rather than process) outcome shows a weaker and less consistent signal, meaning generalizing stewardship's proven benefit to device- and implant-associated infection without adaptation is not well supported by the underlying trials [16,17,12]. Second, the biofilm mechanistic literature and the mature device-infection guideline literature agree that the specific levers stewardship programs use to shorten and narrow therapy, duration reduction, de-escalation on susceptibility, and antibiotic-only management, work against cure in biofilm-associated disease unless paired with adequate source control and, where indicated, biofilm-active combination therapy of guideline-specified duration [13,19,6,28]. Third, the practical path forward evident in both the stewardship implementation literature and the device-infection guidelines is not to exempt biofilm-associated cases from stewardship oversight but to route them through pathway-specific protocols audited on guideline concordance and infectious-diseases consultation rate rather than on generic duration and de-escalation targets, supported by laboratory and surveillance infrastructure able to flag device status and prior debridement [9,15,22].

Several limitations of the underlying evidence temper these conclusions. Few stewardship-effectiveness studies were designed or powered to detect a subgroup effect in biofilm-associated infection, so the inference that generic protocols may underperform here rests on mechanistic plausibility and guideline-literature triangulation more than on head-to-head outcome trials. Antimicrobial resistance trends themselves, tracked at a population level

by surveillance bodies such as the CDC, complicate this picture further, since resistant organisms are simultaneously more likely to require broad-spectrum, cost-intensive regimens and more likely to form biofilms with heightened tolerance, making it difficult in observational data to separate a resistance effect from a biofilm effect on outcome [33,34]. The slow pace of novel antibiotic development against resistant, biofilm-capable organisms over the past decade also narrows the therapeutic options available to any stewardship program managing this population, regardless of how well its protocols are designed [35]. Emerging approaches that target virulence and biofilm formation directly, rather than bacterial viability, and adjunctive host-modulating strategies, remain largely investigational but represent a plausible future complement to antibiotic-centered stewardship for this specific population [36,37,38].

5. Conclusion

Antimicrobial stewardship programs produce well-documented reductions in antimicrobial consumption, resistant-organism incidence, and *C. difficile* infection across general hospital populations, but that evidence base was built predominantly in infections without a biofilm component, and it does not straightforwardly justify applying unmodified duration- and de-escalation-focused protocols to patients with biofilm-associated infection [16,11,12]. The biofilm mechanistic literature and the mature guideline pathways for prosthetic joint, catheter, and cardiac-device infection converge on a different model: source control paired with prolonged, biofilm-active, often combination antibiotic therapy, audited against pathway concordance rather than generic stewardship targets [6,19,28,18]. Programs that build in device-infection-specific protocols, infectious-diseases consultation triggers, and laboratory support capable of flagging biofilm-relevant clinical context are best positioned to extend stewardship's demonstrated benefits to this population without inadvertently undertreating it, and closing the

outcomes-evidence gap for biofilm-associated infection specifically should be a priority for future stewardship program evaluation [9,15,22].

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