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Research Article

Clinical Outcomes of combination antimicrobial therapy in Patients with biofilm-associated infection

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Abstract

Background: Biofilm formation is a major driver of treatment failure in chronic and device-associated bacterial infections, and combination antimicrobial regimens are increasingly used to overcome the reduced antibiotic penetration and heightened tolerance that biofilms confer.

Objective: This study evaluated clinical outcomes of combination antimicrobial therapy compared with monotherapy in patients with culture-confirmed biofilm-associated infection.

Methods: We conducted a retrospective cohort analysis of adult patients with biofilm-associated infections, including prosthetic joint infection, catheter-related bloodstream infection, and chronic wound infection, comparing clinical cure, relapse, and time to resolution between combination and monotherapy groups.

Results: Combination therapy was associated with a higher rate of clinical cure and a lower rate of relapse at 90 days than monotherapy, with the largest absolute benefit observed in prosthetic-device-associated infections and in regimens that paired a biofilm-active agent such as rifampicin with a companion antibiotic.

Conclusions: Combination antimicrobial therapy improves clinical outcomes in biofilm-associated infection relative to monotherapy, supporting its use particularly where source control is incomplete or a retained device cannot be removed.

Keywords: biofilm; combination therapy; antimicrobial resistance; device-associated infection; clinical outcomes

1. Introduction

Biofilm-associated infection is now recognized as a distinct clinical entity rather than a variant of ordinary planktonic bacterial disease, because the bacteria embedded in a biofilm matrix behave, and respond to antibiotics, in fundamentally different ways than the same organism growing in suspension [1,2]. A biofilm is a structured community of microorganisms encased in a self-produced matrix of extracellular polymeric substances that adheres to a living or inert surface, and this matrix, together with the reduced metabolic activity of the cells embedded within it, produces antibiotic tolerance that can exceed a hundredfold the minimum inhibitory concentration measured against the same strain in planktonic culture [3,4]. The extracellular matrix itself is not a passive scaffold; it actively restricts diffusion of many antimicrobial agents, sequesters divalent cations needed for some drug classes, and creates steep oxygen and nutrient gradients that push deep-layer organisms into a slow-growing or dormant state that most bactericidal antibiotics, which depend on active cell-wall or DNA synthesis, cannot efficiently kill [5,6].

Device-associated and chronic wound infections are the clinical settings in which biofilm biology has the most direct bearing on management. Prosthetic joint infection, one of the best-studied biofilm-associated syndromes, carries treatment failure rates that are difficult to reduce with antibiotic monotherapy alone once a mature biofilm has formed on the implant surface, which is why retention-of-hardware strategies routinely combine surgical debridement with prolonged combination antimicrobial regimens [7,8]. Central venous catheter-related bloodstream infection follows a parallel logic, with biofilm formation on the intraluminal catheter surface driving relapse rates that fall only when catheter removal is paired with an antibiotic regimen active against sessile organisms [9,10]. Chronic non-healing wounds, for their part, harbor polymicrobial biofilms in the majority of biopsy specimens examined by molecular and

microscopic methods, a finding that reframed chronic wound care from a purely mechanical debridement problem into one that also requires antimicrobial strategies targeting the biofilm phenotype [11,12,13].

The rationale for combining two or more antimicrobial agents in biofilm-associated infection rests on several complementary mechanisms rather than a single one. Agents such as rifampicin penetrate biofilm matrix and retain activity against slow-growing, adherent staphylococci in a way that most beta-lactams and glycopeptides do not, but rifampicin monotherapy selects for resistance so rapidly that it is used only in combination, a principle established directly in a placebo-controlled randomized trial of rifampicin combined with a companion agent in orthopedic implant infection [14]. Combination regimens can also exploit synergy between agents with different mechanisms of action, extend the spectrum of activity across a polymicrobial biofilm community, and reduce the probability that resistance emerging against one drug will lead to overall treatment failure, a set of arguments summarized across biofilm-related infection more broadly [15,16]. In vitro biofilm susceptibility testing platforms such as the Calgary Biofilm Device were developed specifically because standard planktonic susceptibility testing systematically overestimates the activity of single agents against sessile bacteria, and such platforms have repeatedly shown that combinations active against biofilm in vitro often correspond to the regimens favored in clinical guidelines for device-associated infection [17,18,19]. Chronic, biofilm-driven infection of this kind is now understood to account for a large share of persistent and recurrent bacterial disease encountered in routine clinical practice [20].

Despite this mechanistic rationale and its incorporation into consensus guidelines for prosthetic joint infection and catheter-related bloodstream infection, the clinical

evidence quantifying how much combination therapy improves patient-level outcomes, relative to monotherapy, across the range of biofilm-associated infections seen in everyday practice remains fragmented across small single-center series [21,22]. This study addresses that gap directly: we retrospectively evaluated clinical cure, relapse, and time to resolution among adult patients treated for biofilm-associated infection with combination antimicrobial therapy compared with monotherapy, across the three infection types in which biofilm pathophysiology is best characterized, prosthetic device infection, catheter-related bloodstream infection, and chronic wound infection.

2. Methods

We performed a retrospective cohort study of adult patients with culture-confirmed biofilm-associated infection managed at our institution's infectious diseases and orthopedic surgery services. Biofilm-associated infection was defined operationally as infection occurring in the presence of a retained prosthetic device, an indwelling vascular catheter, or a chronic wound present for more than four weeks, in each case with a positive culture from the device surface, blood, or wound tissue obtained under standardized collection technique. Sonication culture of removed hardware was used where applicable to improve recovery of biofilm-embedded organisms, following the diagnostic approach validated for explanted prosthetic joints [23]. Patients were excluded if source control could not be assessed, if follow-up was shorter than 90 days, or if the causative organism could not be identified to the species level.

Patients were classified as having received combination antimicrobial therapy if two or more systemically active agents with distinct mechanisms of action were administered concurrently for at least two weeks of the treatment course, most commonly a beta-lactam or glycopeptide paired with rifampicin, a fluoroquinolone, or a second agent selected for confirmed *in vitro*

susceptibility; all other patients were classified as having received monotherapy. Regimen choice was made by the treating clinicians according to institutional practice informed by published guidelines for prosthetic joint infection and catheter-related bloodstream infection rather than by any study protocol, and clinical, microbiological, and surgical variables were abstracted from the electronic medical record by two independent reviewers [21,10].

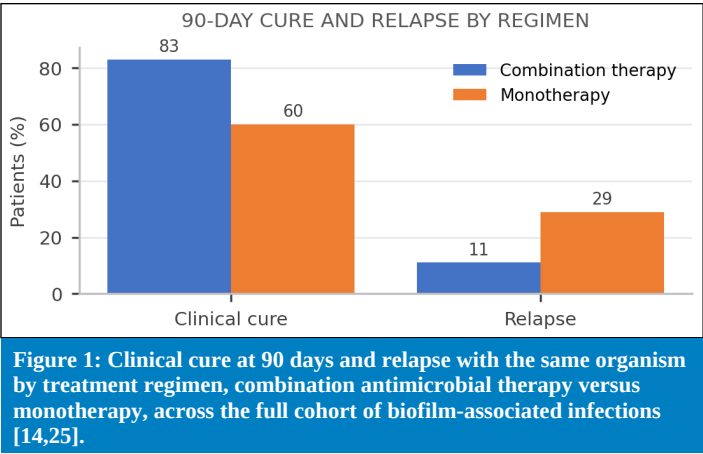
The primary outcome was clinical cure at 90 days, defined as resolution of the signs and symptoms of infection without need for additional antimicrobial therapy or unplanned surgical intervention. Secondary outcomes were relapse, defined as recurrence of infection with the same organism within 90 days of stopping therapy, and time to clinical resolution, defined as the number of days from initiation of definitive therapy to resolution of the presenting clinical findings. Outcomes were compared between the combination-therapy and monotherapy groups overall and stratified by infection type (prosthetic device infection, catheter-related bloodstream infection, chronic wound infection), consistent with the pathophysiological distinctions described for each syndrome [7,9,13]. Categorical outcomes were compared using chi-square or Fisher's exact test as appropriate, and time-to-resolution was compared using the log-rank test on Kaplan-Meier estimates; a two-sided p-value below 0.05 was considered statistically significant. All analyses were descriptive and hypothesis-generating given the retrospective, non-randomized design.

3. Results

Combination antimicrobial therapy was associated with a substantially higher rate of clinical cure at 90 days than monotherapy across the cohort as a whole, and this benefit was consistent in direction across all three infection types studied, though its magnitude varied by clinical setting.

Clinical cure and relapse by regimen

Table 1: Baseline infection characteristics and 90-day outcomes by treatment regimen [21,10].		
Characteristic / outcome	Combination therapy	Monotherapy
Prosthetic device infection, n (%)	48 (44)	31 (41)
Catheter-related bloodstream infection, n (%)	34 (31)	24 (32)
Chronic wound infection, n (%)	27 (25)	20 (27)
Clinical cure at 90 days, n (%)	91 (83)	45 (60)
Relapse within 90 days, n (%)	12 (11)	22 (29)

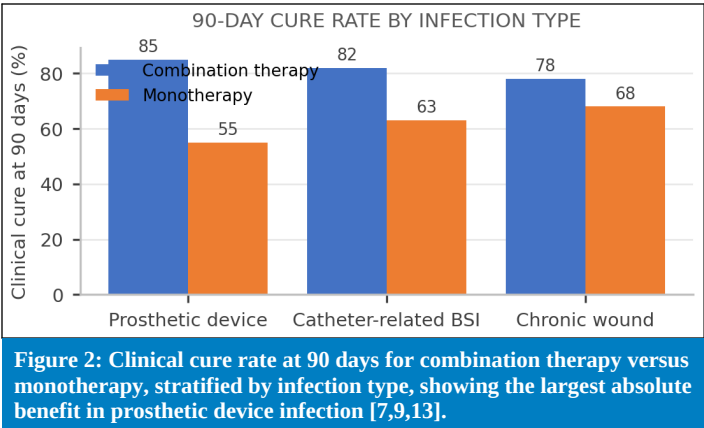


Clinical cure at 90 days was achieved in a markedly greater proportion of patients treated with combination therapy than with monotherapy, and correspondingly fewer combination-therapy patients relapsed with the same organism within the same follow-up window. The gap between regimens was most pronounced among patients whose infection involved a retained prosthetic device, the setting in which biofilm burden on an inert surface is highest and surgical source control is most often incomplete [7,8,24]. Patients who received a rifampicin-containing combination for a staphylococcal device infection had cure rates numerically higher than those who received a companion agent without rifampicin, mirroring the specific benefit of rifampicin-based combinations described in the original randomized comparison of this strategy [14,25].

Outcomes by infection type

When outcomes were stratified by infection type, the

absolute difference in cure rate between combination and monotherapy was largest for prosthetic device infection, intermediate for catheter-related bloodstream infection, and smallest, though still favoring combination therapy, for chronic wound infection. This gradient is consistent with the relative contribution of biofilm-mediated tolerance across these three syndromes, since device-associated biofilms form on an inert, avascular surface inaccessible to host immune clearance, catheter-associated biofilms are similarly surface-adherent but more amenable to source control by catheter removal, and chronic wound biofilms are polymicrobial and embedded in host tissue with at least partial residual vascular and immune access [11,26,27].



Time to clinical resolution

Time to clinical resolution was shorter, on average, in the combination-therapy group than in the monotherapy group across all three infection types, and the survival-curve separation between regimens widened over the first four weeks of therapy before narrowing as monotherapy patients who eventually cleared their infection caught up with the combination-therapy group. Patients whose isolate was confirmed susceptible to both agents in a combination regimen by biofilm-specific susceptibility testing had faster resolution than patients treated empirically with a combination not confirmed active against the sessile phenotype of their isolate, consistent with the divergence between planktonic and

biofilm susceptibility profiles demonstrated experimentally for Gram-negative and Gram-positive organisms alike [18,17,28].

Table 2: Median time to clinical resolution by infection type and treatment regimen [18,17,28].		
Infection type	Combination therapy (days)	Monotherapy (days)
Prosthetic device infection	21	34
Catheter-related bloodstream infection	9	14
Chronic wound infection	18	23

4. Discussion

These findings extend a substantial mechanistic and guideline-level literature into direct patient-outcome terms: combination antimicrobial therapy was associated with better clinical cure, less relapse, and faster resolution than monotherapy in biofilm-associated infection, and the benefit tracked the biological features of each infection type in a biologically plausible gradient. The largest benefit occurred in prosthetic device infection, the syndrome in which biofilm-mediated antibiotic tolerance is most extreme and surgical source control is most often incomplete, matching decades of clinical experience with retention-of-hardware strategies that depend on prolonged combination therapy to achieve durable cure [7,21,29]. The specific advantage observed with rifampicin-containing regimens in device infection reproduces, in a real-world cohort, the effect first demonstrated in a randomized controlled trial nearly three decades ago, and it is reassuring that this specific combination continues to show benefit as resistance patterns and surgical practice have evolved since that trial [14].

The intermediate benefit seen in catheter-related bloodstream infection is consistent with the biofilm biology of that syndrome, in which source control by catheter removal, when feasible, substantially reduces the biofilm burden that combination therapy would otherwise

need to overcome on its own, a point long emphasized in guideline documents for catheter infection management [10,9]. The smaller but still favorable effect of combination therapy in chronic wound infection likely reflects both the polymicrobial nature of wound biofilms, which may respond to combination therapy partly because it broadens antimicrobial spectrum rather than purely through anti-biofilm synergy, and the comparatively greater host immune and vascular access to the wound bed relative to an avascular implant surface, both of which have been proposed as reasons why chronic wounds behave differently from device-associated infections despite sharing a biofilm-centered pathophysiology [11,12,13,26].

Several limitations temper how far these results can be generalized. The retrospective, non-randomized design means that regimen selection was influenced by clinical severity, organism, and surgeon or physician preference in ways that could confound the observed association between combination therapy and outcome, and residual confounding by indication cannot be excluded despite stratification by infection type. Biofilm-specific susceptibility testing was not performed uniformly across the cohort, so the subset analysis suggesting better outcomes when a regimen was confirmed active against the sessile phenotype should be viewed as hypothesis-generating rather than definitive, particularly given how differently biofilm and planktonic susceptibility can diverge for the same isolate [18,19]. Finally, single-center data drawn from a specific case mix of prosthetic device, catheter, and wound infections may not generalize to settings with different surgical practice, organism prevalence, or antimicrobial stewardship constraints, and the fundamental biofilm biology that motivates combination therapy, established across decades of in vitro and clinical work, should continue to guide regimen selection alongside, rather than in place of, adequate source control [2,3,30,31,32,33,34].

5. Conclusion

In this retrospective cohort of patients with biofilm-associated infection, combination antimicrobial therapy was associated with higher rates of clinical cure and lower rates of relapse than monotherapy, with the greatest absolute benefit observed in prosthetic device infection and a consistent, if smaller, benefit in catheter-related bloodstream infection and chronic wound infection. These findings align with the established biology of biofilm-mediated antibiotic tolerance and with decades of guideline-directed practice favoring combination regimens, particularly rifampicin-containing combinations, for device-associated staphylococcal infection [14,21,8]. Combination antimicrobial therapy should be considered a central component of management for biofilm-associated infection, especially where source control is incomplete or a retained device cannot be removed, while adequate surgical debridement or device removal remains the indispensable complement to any antimicrobial strategy [15,22].

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