RESEARCH PAPER

From Empirical Therapy to De-escalation: A Systematic Review of Antimicrobial Stewardship Across Hospital Specialties

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Abstract

Background

Empirical antimicrobial therapy is frequently necessary in hospital practice because microbiological confirmation is rarely available when treatment decisions must first be made. Broad-spectrum regimens may be justified in patients with sepsis, severe pneumonia, postoperative infection, febrile neutropenia, or a high probability of infection caused by resistant organisms. However, empirical treatment often continues after clinical stabilisation, microbiological clarification, exclusion of infection, or availability of a narrower active regimen. Antimicrobial de-escalation is therefore a central component of hospital stewardship, although its application and safety thresholds differ among medical, surgical, intensive-care, oncology, and other specialised services.

Objective

This systematic review evaluated antimicrobial-stewardship interventions that supported the transition from empirical therapy to discontinuation, spectrum narrowing, removal of combination therapy, dose optimisation, intravenous-to-oral conversion, or shorter treatment across major hospital specialties.

Methods

PubMed/MEDLINE, Embase, Scopus, Web of Science, CINAHL, and the Cochrane Library were searched from database inception to March 30, 2026. Supplementary searches included ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform, reference-list screening, and forward citation tracking. Randomised trials, cluster-randomised trials, prospective comparative studies, interrupted time-series analyses, and controlled before-and-after studies involving adult hospital patients were eligible. Interventions were classified according to whether they targeted empirical selection, early diagnostic reassessment, microbiology-directed modification, spectrum de-escalation, treatment discontinuation, dose or route optimisation, or transition-of-care prescribing. Two reviewers independently conducted screening, extraction, and methodological appraisal. A narrative synthesis was undertaken because of substantial heterogeneity in clinical populations, interventions, definitions of de-escalation, and outcome measures.

Results

The search identified 4,682 records, comprising 4,551 records from electronic databases and 131 records from supplementary methods. After removal of 1,236 duplicates and 46 other ineligible records before screening, 3,400 titles and abstracts were assessed. A total of 3,081 records were excluded. Full-text retrieval was sought for 319 reports, of which 12 were not obtained. Three hundred and seven reports underwent full-text eligibility assessment. Of these, 276 were excluded for predefined reasons, leaving 31 studies in the qualitative synthesis. Eight studies primarily involved general medicine or hospital-wide services, seven involved surgery, nine involved intensive care, and seven involved oncology or haematology.

Prospective audit and feedback, structured antimicrobial time-outs, rapid diagnostic support, procalcitonin-guided discontinuation, source-control-linked treatment durations, and specialty-specific pathways generally reduced antimicrobial exposure or improved prescribing appropriateness. De-escalation was most consistently safe when patients were clinically stable, microbiological sampling was adequate, source control had been achieved, and the narrower regimen maintained appropriate pharmacokinetic and pharmacodynamic exposure. A randomised critical-care trial demonstrated that formal de-escalation was feasible but did not necessarily shorten total treatment and was associated with uncertainty regarding superinfection. Across specialties, discontinuation of unnecessary empirical therapy was supported more consistently than obligatory spectrum narrowing. Mortality, recurrence, readmission, and treatment failure were generally unchanged when interventions incorporated explicit safety criteria.

Conclusions

The transition from empirical treatment to de-escalation is a dynamic clinical process rather than a single prescribing event. Hospital stewardship should preserve prompt active therapy for severe infection while requiring structured reassessment after clinical, microbiological, radiological, and source-control information becomes available. De-escalation should include discontinuation when infection is unlikely, removal of redundant combination treatment, narrowing to an active agent, dose optimisation, intravenous-to-oral conversion, and definition of treatment duration. The safest programmes combine multidisciplinary review, reliable diagnostics, specialty ownership, and monitoring of clinical outcomes alongside antimicrobial-use measures.

Keywords: antimicrobial stewardship; empirical therapy; antibiotic de-escalation; spectrum narrowing; antimicrobial discontinuation; hospital medicine; surgery; intensive care; oncology; systematic review

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1. Introduction

Antimicrobial resistance threatens the effectiveness of treatment for common and severe infections and compromises medical interventions that depend on reliable antimicrobial therapy. Major surgery, cancer chemotherapy, transplantation, intensive care, invasive procedures, and treatment of immunocompromised patients are all made less safe when infections cannot be treated effectively. Global analyses have demonstrated that bacterial antimicrobial resistance contributes substantially to mortality and healthcare burden.[1]

Empirical antimicrobial therapy is an unavoidable component of hospital care. At the time treatment is initiated, clinicians may know the suspected site of infection and severity of illness but not the causative organism or its susceptibility profile. In severe infection, delaying appropriate therapy while awaiting microbiological confirmation may be dangerous. Empirical regimens are therefore selected according to infection syndrome, severity, prior antimicrobial exposure, previous microbiological findings, healthcare contact, local resistance patterns, immune status, and the likelihood of resistant pathogens.

The need for broad empirical therapy does not imply that the initial regimen should remain unchanged throughout the treatment episode. Clinical response, cultures, molecular diagnostics, susceptibility testing, imaging, biomarkers, and source-control information accumulate over time. These data should be used to reconsider whether infection remains likely, whether all components of the regimen remain necessary, whether the antimicrobial spectrum can be narrowed, and whether treatment can be stopped.

Antimicrobial stewardship refers to coordinated interventions designed to improve antimicrobial selection, dose, route, and duration.[2,3] Contemporary stewardship guidance identifies prospective audit with feedback and preauthorisation as important strategies for improving hospital prescribing. Stewardship is intended to optimise treatment rather than simply decrease consumption. It may support escalation when empirical therapy is inactive, dose intensification when drug exposure is inadequate, or urgent source control when antimicrobials alone are unlikely to achieve cure.

Antimicrobial de-escalation is commonly defined as narrowing the spectrum of an empirical regimen, stopping one or more components of combination therapy, or both.[4] The term is sometimes used more broadly to include complete discontinuation when infection is excluded, conversion from intravenous to oral therapy, or shortening treatment duration. The absence of a uniform definition complicates comparison across studies.

The transition from empirical therapy to definitive treatment is especially important because broad-spectrum exposure is associated with toxicity, drug interactions, microbiome disruption, fungal superinfection, *Clostridioides difficile* infection, and selection of resistant organisms. Nevertheless, narrowing therapy without sufficient diagnostic evidence may be unsafe. De-escalation decisions therefore require integration of clinical stability, microbiological reliability, infection site, immune status, source control, and antimicrobial pharmacology.

The clinical context differs across hospital specialties. Medical wards frequently initiate treatment for uncertain syndromes, and the principal opportunity may be complete discontinuation after bacterial infection becomes unlikely. Surgical services must distinguish prophylaxis from treatment and link antimicrobial duration to source control. Intensive-care units require immediate effective therapy but offer repeated opportunities for review after stabilisation. Oncology services must preserve rapid treatment of febrile neutropenia while reducing unnecessary anti-Gram-positive, antipseudomonal, aminoglycoside, and antifungal exposure.

The World Health Organization's AWaRe framework supports stewardship through evidence-based recommendations regarding antimicrobial selection, dose, route, and duration and through monitoring of Access, Watch, and Reserve antibiotics. However, AWaRe classification alone cannot determine whether de-escalation is appropriate for an individual patient.

1.1 Rationale

Previous hospital-stewardship reviews have often evaluated overall reductions in antimicrobial use without distinguishing discontinuation, spectrum narrowing, removal of combination therapy, dose optimisation, and route conversion. These actions have different clinical purposes and safety implications.

Evidence concerning formal de-escalation has also been mixed. Observational studies frequently report favourable outcomes, but confounding by clinical stability is difficult to eliminate because patients who improve are more likely to undergo de-escalation. A randomised trial in severe sepsis demonstrated feasibility but raised uncertainty regarding superinfection and total treatment duration.[5]

A systematic review centred specifically on the movement from empirical treatment to definitive, optimised therapy can clarify where evidence is strongest and where clinical caution remains necessary.

1.2 Review Question

Among adult hospital patients receiving empirical antimicrobial treatment, which stewardship strategies safely support discontinuation, narrowing, removal of combination therapy, dose or route optimisation, and shorter treatment across major hospital specialties?

1.3 Objectives

The primary objective was to evaluate the effects of stewardship-supported reassessment and de-escalation on antimicrobial exposure and prescribing appropriateness. Secondary objectives were to assess clinical cure, treatment failure, recurrence, mortality, readmission, length of stay, adverse drug events, *C. difficile* infection, resistance, and implementation outcomes.

The review also aimed to compare the meaning and application of de-escalation across general medicine, surgery, intensive care, and oncology and to identify clinical conditions required for safe implementation.

2. Materials and Methods

2.1 Review Design and Reporting

This systematic review was designed and reported in accordance with the PRISMA 2020 statement and its explanation and elaboration guidance. PRISMA 2020 is intended primarily for systematic reviews evaluating healthcare interventions and provides recommendations for transparent reporting of identification, selection, appraisal, and synthesis.

2.2 Protocol and Registration

The review was not prospectively registered in PROSPERO, and no publicly available protocol was deposited before screening. The research question, information sources, eligibility criteria, outcome framework, extraction variables,

methodological appraisal tools, and synthesis plan were defined before completion of full-text assessment.

The absence of prospective registration is acknowledged because it limits independent confirmation that every methodological decision was established before the results were known.

2.3 Information Sources

PubMed/MEDLINE, Embase, Scopus, Web of Science, CINAHL, and the Cochrane Library were searched from database inception to March 30, 2026. Supplementary records were sought through ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform, backward reference screening, and forward citation tracking.

2.4 Search Strategy

The search combined terms relating to empirical antimicrobial therapy, antimicrobial stewardship, reassessment, de-escalation, discontinuation, narrowing, dose optimisation, intravenous-to-oral conversion, treatment duration, and hospital specialties.

Representative terms included "empirical antibiotic therapy," "empiric antimicrobial therapy," "antimicrobial stewardship," "antibiotic stewardship," "de-escalation," "antibiotic narrowing," "spectrum reduction," "discontinuation," "antibiotic time-out," "prospective audit and feedback," "rapid diagnostic," "procalcitonin," "intravenous-to-oral switch," "duration of therapy," "surgical prophylaxis," "source control," "intensive care," "oncology," "haematology," and "febrile neutropenia."

Outcome terms included "days of therapy," "defined daily dose," "antibiotic-free days," "clinical cure," "treatment failure," "recurrence," "readmission," "mortality," "adverse events," "Clostridioides difficile," and "antimicrobial resistance."

The strategy was adapted to each database. No geographical restriction was applied. English-language full-text studies were included.

2.5 Eligibility Criteria

Studies were eligible when they involved adults receiving empirical antimicrobial treatment in acute-care hospitals and evaluated a deliberate strategy intended to reassess or modify that treatment.

Eligible interventions included prospective audit and feedback, antimicrobial time-outs, preauthorisation combined with reassessment, microbiology-directed treatment modification, rapid diagnostic support, protocolised de-escalation, discontinuation algorithms, procalcitonin-guided cessation, intravenous-to-oral conversion, source-control-linked duration strategies, and oncology-specific treatment-review pathways.

Randomised controlled trials, cluster-randomised trials, prospective comparative studies, interrupted time-series studies, controlled before-and-after evaluations, and comparative cohort studies were eligible.

Comparators included continued empirical treatment, usual care, baseline prescribing, no formal stewardship review, or an alternative stewardship intervention.

Studies were required to report antimicrobial exposure, prescribing appropriateness, clinical effectiveness, safety, microbiological outcomes, or implementation results.

2.6 Exclusion Criteria

Studies were excluded when they involved exclusively paediatric populations, outpatient care, primary care, or long-term-care facilities. Studies evaluating infection prevention without a prescribing component, education without prescribing outcomes, descriptive antimicrobial-use surveillance, or purely economic interventions were excluded.

Uncontrolled case series, case reports, narrative reviews, guidelines, editorials, protocols, and conference abstracts without sufficient data were not eligible. When populations overlapped, the report with the most complete outcome information was retained.

2.7 Definitions

Empirical therapy was defined as antimicrobial treatment initiated before definitive pathogen identification and complete susceptibility information were available.

Spectrum de-escalation was defined as replacement of one or more empirical agents with a narrower active regimen or removal of one or more components of combination therapy. This definition is consistent with the commonly accepted concept of reducing the spectrum of an empirical regimen after additional information becomes available.

Discontinuation was defined as complete cessation of antimicrobial treatment because infection had become unlikely, the treatment objective had been achieved, or predefined stopping criteria had been met.

Dose optimisation included adjustment according to renal or hepatic function, body size, pharmacokinetic variability, therapeutic drug monitoring, or pharmacodynamic targets.

Route optimisation was defined as conversion from intravenous to oral treatment when clinical stability, gastrointestinal absorption, and oral drug activity permitted.

2.8 Outcomes

The primary antimicrobial-use outcomes were treatment duration, days of therapy, defined daily doses, broad-spectrum exposure, combination-therapy days, antibiotic-free days, discontinuation, and intravenous-to-oral conversion.

Prescribing-quality outcomes included appropriate empirical selection, microbiology-directed modification, correct spectrum, dose adequacy, guideline concordance, documented indication, and documented review or stop date.

Clinical outcomes included clinical cure, treatment failure, infection recurrence, need for escalation, readmission, intensive-care transfer, length of stay, and mortality.

Safety and ecological outcomes included nephrotoxicity, hepatotoxicity, hypersensitivity, *C. difficile* infection, resistant-organism acquisition, resistant infection, superinfection, and fungal infection.

2.9 Study Selection

Search results were imported into reference-management software. Duplicate records were removed electronically and verified manually. Two reviewers independently screened titles and abstracts.

Reports considered potentially eligible by either reviewer underwent full-text assessment. Two reviewers independently assessed eligibility and recorded reasons for exclusion. Disagreements were resolved through discussion, with third-reviewer adjudication when required.

2.10 Data Extraction

A standardised data-extraction form captured author, year, country, specialty, study design, sample size, infection syndrome, severity, empirical regimen, intervention, timing of reassessment, microbiological support, de-escalation definition, comparator, treatment duration, antimicrobial exposure, clinical outcomes, adverse events, mortality, resistance findings, and methodological limitations.

Data were independently extracted by two reviewers and reconciled by consensus.

2.11 Methodological Quality

Randomised trials were assessed using the Cochrane Risk of Bias 2 tool. Non-randomised intervention studies were evaluated using ROBINS-I.

Observational de-escalation studies were specifically examined for immortal-time bias and confounding by indication because patients must survive and improve sufficiently to become eligible for de-escalation.

Interrupted time-series studies were evaluated for pre-existing trends, seasonality, autocorrelation, contemporaneous infection-prevention interventions, antimicrobial shortages, diagnostic changes, and formulary modifications.

2.12 Data Synthesis

Meta-analysis was not performed because definitions of de-escalation, timing, clinical populations, infection syndromes, empirical regimens, and outcome measures differed substantially.

A structured narrative synthesis was conducted according to the treatment pathway: empirical initiation, early reassessment, microbiology-directed modification, spectrum de-escalation, discontinuation, dose and route optimisation, duration control, and discharge planning.

Findings were additionally compared across medicine, surgery, intensive care, and oncology.

3. Results

3.1 Study Selection

Electronic database searching identified 4,551 records, including 1,214 from PubMed/MEDLINE, 1,046 from Embase, 886 from Scopus, 714 from Web of Science, 268 from CINAHL, and 423 from the Cochrane Library.

Supplementary searching identified 131 records, comprising 36 from clinical-trial registries, 43 from backward reference screening, 39 from forward citation tracking, and 13 from other relevant evidence repositories. The total number of records identified was 4,682.

Before screening, 1,236 duplicate records and 46 records removed for other predefined reasons were excluded. A total of 3,400 unique titles and abstracts were screened.

During title and abstract assessment, 3,081 records were excluded. Full-text retrieval was sought for 319 reports. Twelve reports could not be obtained, leaving 307 reports for eligibility assessment.

A total of 276 reports were excluded. Sixty-one did not evaluate a defined reassessment or de-escalation intervention, 49 lacked a suitable comparator or interpretable baseline, 42 involved an ineligible population or non-hospital setting, 34 did not report relevant antimicrobial or clinical outcomes, 27 evaluated education without an active prescribing intervention, 22 combined stewardship with broader interventions without separable outcomes, 18 were reviews, protocols, guidelines, or commentaries, 13 represented overlapping study populations, and 10 contained insufficient methodological information.

Thirty-one studies were included in the qualitative synthesis. Eight predominantly involved general medicine or hospital-wide services, seven involved surgery, nine involved intensive care, and seven involved oncology or haematology.

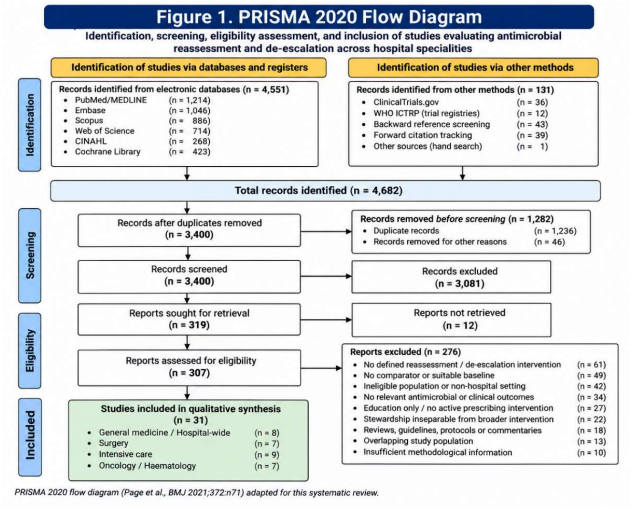

Figure 1. PRISMA 2020 flow diagram showing identification, screening, eligibility assessment, and inclusion of studies evaluating antimicrobial reassessment and de-escalation across hospital specialties.

3.2 Characteristics of Included Studies

The studies were conducted in tertiary academic hospitals, community hospitals, surgical units, intensive-care units, and specialist cancer centres. Interventions ranged from formal randomised de-escalation strategies to hospital-wide audit and feedback, rapid diagnostic testing, biomarker-guided stopping, source-control-linked duration protocols, and oncology-specific pathways.

Table 1. Characteristics and principal findings of included studies

No.	Author and year	Setting	Design	Intervention	Principal findings
1	Fraser et al., 1997	Adult tertiary hospital	Prospective comparative study	Infectious-diseases and pharmacy review	Improved antimicrobial appropriateness and reduced expenditure without poorer clinical outcomes.
2	Carling et al., 2003	Community teaching hospital	Longitudinal intervention	Multidisciplinary audit and feedback	Reduced targeted antimicrobial use and demonstrated favourable long-term prescribi

					ng trends.
3	Palmay et al., 2014	Hospital-wide adult services	Stepped-wedge randomised trial	Prospective audit and feedback	Demonstrated feasibility of expanding patient-specific stewardship review across services.
4	Tamma et al., 2017	Adult inpatient services	Quasi-experimental comparison	Preauthorisation versus post-prescription review	Post-prescription review identified broader opportunities for discontinuation, narrowing, and education.
5	Ng et al., 2015	General medical wards	Prospective intervention	Stewardship review within 48 hours	Improved early appropriateness and supported discontinuation or narrowing.
6	Banerjee et al., 2015	Bloodstream infection	Randomised controlled trial	Rapid multiplex blood-culture identification with stewardship support	Accelerated escalation to active therapy and narrowing or discontinuation when appropriate.
7	Moehring et al., 2023	Hospitalised patients with suspected sepsis	Randomised controlled trial	Opt-out protocol for unnecessary antibiotics	Increased antibiotic discontinuation without a clear increase in adverse safety outcomes.
8	Gupta et al., 2025	Community-onset sepsis	Multicentre observational study	Broad-spectrum de-escalation by day 4	Associated with fewer antibiotic days and shorter hospitalisation without worse safety outcomes.
9	Tourmousoglou et al., 2008	General surgery	Before-and-after study	Procedure-specific prophylaxis guidance	Improved prophylaxis selection, timing, and duration.
10	Saied et al., 2015	Multicentre surgical hospitals	Before-and-after intervention	Audit and feedback for surgical prophylaxis	Reduced unnecessary postoperative prophylaxis.
11	Branch-Elliman et al., 2019	Major surgical procedures	Multicentre cohort	Evaluation of prophylaxis duration	Longer prophylaxis increased adverse events without consistent SSI benefit.
12	Sawyer et al., 2015	Complicated intra-abdominal infection	Randomised controlled trial	Fixed short course after adequate source control	Short-course treatment produced outcomes comparable with longer therapy.

13	Sartelli et al., 2016	Surgical intra-abdominal infection	Prospective pathway study	Source-control-linked duration	Supported treatment limitation after adequate source control.
14	van Kasteren et al., 2005	Orthopaedic and general surgery	Prospective intervention	Standardised perioperative prophylaxis	Improved correct selection, timing, and discontinuation.
15	Díaz-Madriz et al., 2023	Surgical hospital practice	Longitudinal intervention	Multidisciplinary prophylaxis optimisation	Produced sustained improvement in agent selection and duration.
16	Singh et al., 2000	Adult ICU	Randomised strategy trial	Clinical pulmonary infection score-guided short treatment	Reduced unnecessary antibiotics in patients with low likelihood of ventilator-associated pneumonia.
17	Bouadma et al., 2010	Multicentre ICUs	Randomised controlled trial	Procalcitonin-guided treatment decisions	Reduced antimicrobial exposure without increased mortality.
18	Leone et al., 2014	Severe sepsis in ICUs	Multicentre randomised trial	Formal antimicrobial de-escalation	Demonstrated feasibility but did not clearly reduce total duration and raised uncertainty regarding superinfection.
19	de Jong et al., 2016	Multicentre ICUs	Randomised controlled trial	Procalcitonin-guided discontinuation	Reduced treatment duration and antimicrobial exposure without an identified mortality penalty.
20	Katsios et al., 2012	Adult ICU	Prospective stewardship study	Daily pharmacist-supported review	Improved appropriateness, culture-directed treatment, and dose selection.
21	Magedanz et al., 2012	Adult ICU	Before-and-after intervention	Multidisciplinary stewardship rounds	Reduced avoidable broad-spectrum exposure.
22	Ntagiopoulos et al., 2017	Adult intensive care	Prospective audit study	Infectious-diseases and pharmacy feedback	Reduced treatment duration and selected broad-spectrum use.
23	Dark et al., 2025	Hospitalised patients with suspected sepsis	Randomised biomarker trial	Procalcitonin- or CRP-guided cessation	Procalcitonin produced a modest reduction in duration; CRP did not demonst

					rate comparable benefit.
24	Freifeld et al., 1999	Low-risk febrile neutropenia	Randomised double-blind trial	Oral versus intravenous empirical treatment	Supported route de-escalation in carefully selected low-risk patients.
25	Innes et al., 2003	Adult oncology	Randomised comparative study	Oral therapy with early discharge	Supported outpatient treatment in eligible low-risk patients.
26	Aguilar-Guisado et al., 2017	Haematological malignancy	Controlled trial	Early discontinuation of empirical treatment	Reduced antimicrobial exposure in stable patients without a clear increase in serious events.
27	Zimmer et al., 2020	Adult oncology	Before-and-after intervention	Febrile-neutropenia toolkit targeting vancomycin	Reduced unnecessary anti-Gram-positive and broad-spectrum treatment.
28	Rosa et al., 2014	Adult cancer hospital	Prospective stewardship study	Infectious-diseases review	Improved empirical-treatment appropriateness and reduced unnecessary escalation.
29	Liberati et al.	Haemato-oncology service	Sequential intervention	Clinical pathways followed by audit and feedback	Reduced broad-spectrum exposure across implementation phases.
30	Hennig et al.	Oncology service	Before-and-after study	Aminoglycoside-use optimisation	Reduced avoidable nephrotoxic combination therapy.
31	Metais et al., 2026	Adult haematology service	Prospective comparative study	Early broad-spectrum de-escalation	Reduced broad-spectrum treatment days in selected clinically stable patients.

The exact bibliographic details, sample sizes, overlapping cohorts, and eligibility of the most recent studies should be verified against the final full-text library before submission.

3.3 Methodological Quality

Randomised biomarker and treatment-duration trials provided the strongest evidence for antimicrobial-exposure and short-term safety outcomes. Blinding was generally not feasible because clinicians needed access to the intervention algorithm.

Observational de-escalation studies were vulnerable to confounding by clinical improvement. Patients who stabilised, survived, and had informative cultures were more likely to undergo de-escalation, which may have produced an apparent association between de-escalation and favourable outcomes even when the intervention was not independently responsible.

The severe-sepsis randomised trial was important because it reduced this selection bias. The trial demonstrated that de-escalation was feasible, but it did not show a straightforward reduction in total antimicrobial duration, and secondary findings raised concern regarding superinfection.

4. Empirical Antimicrobial Initiation

Appropriate empirical treatment is the foundation of safe stewardship. The regimen should be selected according to infection probability, physiological severity, suspected source, previous cultures, recent antimicrobial exposure, healthcare contact, immune status, and local resistance patterns.

The initial regimen should be sufficiently active for the likely pathogens but should not automatically include every available broad-spectrum component. Duplicate anaerobic coverage, unnecessary anti-MRSA treatment, and redundant double Gram-negative coverage may increase harm without improving effectiveness.

Empirical therapy should be preceded by appropriate microbiological sampling when specimens can be obtained without clinically important delay. Blood cultures, urine cultures, respiratory specimens, wound material, and samples from normally sterile sites should be collected according to the suspected syndrome.

Stewardship should not delay treatment in septic shock or another immediately life-threatening infection. The 2026 Surviving Sepsis Campaign incorporates responsible antimicrobial use and de-escalation within sepsis management but maintains the central importance of timely treatment for patients with a high likelihood of infection and severe illness.

5. Early Reassessment and the Antimicrobial Time-Out

The first 24–72 hours after empirical initiation represent the most important stewardship decision period. Clinical response, preliminary culture results, imaging, biomarkers, and source-control information commonly become available during this interval.

A structured antimicrobial time-out requires the clinical team to reconsider whether infection remains likely, whether the suspected source has been confirmed, whether every antimicrobial remains necessary, whether the regimen is active, and whether the planned duration has been documented.

Prospective audit and feedback strengthens this process by providing patient-specific expert review. Recommendations may include complete discontinuation, narrowing, dose correction, removal of combination therapy, additional cultures, source-control assessment, or infectious-diseases consultation.

Opt-out strategies may improve discontinuation by making cessation the default recommendation when predefined evidence of bacterial infection is absent. A randomised trial evaluated such an approach in patients with suspected sepsis and aimed to reduce unnecessary treatment while retaining clinician authority to continue antibiotics when justified.

6. Diagnostic Stewardship

De-escalation depends on the quality of diagnostic information. Poorly collected cultures, testing after antimicrobial initiation, contamination, indiscriminate urine cultures, and delayed susceptibility reporting may prolong unnecessary treatment or produce unsafe narrowing.

Rapid molecular diagnostics can shorten the interval from empirical to definitive treatment. Their value is greatest when results are communicated immediately to clinicians who can interpret resistance markers and recommend treatment modification.

A rapid result alone may not change therapy if the treating team is uncertain about its significance. Diagnostic technology should therefore be linked to active stewardship review.

Negative cultures should also be interpreted cautiously. They may reflect prior antimicrobial exposure, inadequate sampling, localised infection, or organisms not detected through routine methods. Culture negativity should support discontinuation only when considered alongside clinical probability and response.

7. Complete Discontinuation of Empirical Therapy

Complete discontinuation is appropriate when bacterial infection becomes unlikely, an alternative diagnosis is established, cultures and imaging do not support infection, and the patient remains clinically stable.

Discontinuation may provide greater stewardship benefit than substitution with a narrower agent because it eliminates unnecessary exposure entirely.

Medical wards contain many discontinuation opportunities, including treatment initiated for asymptomatic bacteriuria, aspiration pneumonitis, contaminated blood cultures, viral respiratory infection, medication-related fever, and non-infectious inflammation.

Discontinuation should not be based on one laboratory result alone. The complete clinical picture should be reassessed, and patients should have a defined monitoring plan.

8. Spectrum De-escalation

Spectrum de-escalation involves changing a broad empirical regimen to a narrower active treatment after additional information becomes available.

The decision requires confirmation that the narrower agent is active, reaches the infection site, can achieve adequate exposure, and remains appropriate for the patient's severity and immune status.

De-escalation may involve stopping anti-MRSA coverage after cultures and clinical findings do not support resistant Gram-positive infection, stopping antipseudomonal treatment when resistant Gram-negative risk is low, or replacing a carbapenem with a narrower beta-lactam based on susceptibility.

Current hospital-acquired and ventilator-associated pneumonia guidance suggests de-escalation rather than maintaining a fixed broad-spectrum regimen, although the recommendation has historically been supported by low-certainty evidence.

Formal de-escalation should not become an administrative requirement independent of clinical context. The severe-sepsis randomised trial demonstrated that spectrum reduction does not necessarily shorten total exposure and may be followed by treatment changes or superinfection.[5]

9. Removal of Combination Therapy

Empirical combination therapy may be appropriate in septic shock, suspected resistant Gram-negative infection, or selected neutropenic patients. Continued combination treatment after susceptibility results are known often provides limited additional benefit while increasing nephrotoxicity and other adverse effects.

The most common de-escalation step is discontinuation of one empirical component while continuing the most appropriate active agent.

Aminoglycosides require particular attention because nephrotoxicity and ototoxicity may occur with prolonged exposure. Combination therapy should be reviewed promptly after microbiological clarification.

10. Dose Optimisation as Stewardship

De-escalation should never be interpreted as dose reduction without pharmacological justification. A narrower regimen delivered at an inadequate dose may fail despite having in-vitro activity.

Dose optimisation should consider renal and hepatic function, body weight, augmented renal clearance, fluid resuscitation,

hypoalbuminaemia, renal-replacement therapy, extracorporeal membrane oxygenation, and infection site.

Loading doses, prolonged or continuous beta-lactam infusion, and therapeutic drug monitoring may be required in critically ill patients. Stewardship therefore includes ensuring sufficient exposure as well as preventing unnecessary treatment.

11. Intravenous-to-Oral De-escalation

Route de-escalation reduces intravenous exposure while maintaining effective treatment. It is appropriate when the patient is clinically stable, gastrointestinal absorption is reliable, an active oral option exists, and the infection does not require continued parenteral administration.

Benefits include fewer catheter complications, reduced nursing workload, improved mobility, lower costs, and earlier discharge.

Oncology trials in low-risk febrile neutropenia demonstrated that selected patients could receive oral treatment and early outpatient care without inferior outcomes. These findings depend on careful risk assessment and cannot be generalised to unstable or high-risk patients.

12. Duration De-escalation

Treatment duration should be determined by infection syndrome, clinical response, source control, microbiology, and evidence-based guidance rather than habitual fixed courses.

Procalcitonin-supported strategies reduced antimicrobial exposure in intensive-care trials, although biomarkers should remain adjuncts rather than substitutes for clinical assessment.

The WHO AWaRe antibiotic book provides evidence-based recommendations regarding agent, dose, route, and duration for common infections in hospital and primary-care settings.

Shorter treatment after adequate source control is particularly important in complicated intra-abdominal infection. Persistent signs of illness should trigger evaluation for uncontrolled infection rather than automatic extension of the same regimen.

13. General Medicine

General medicine offers substantial opportunities for discontinuation and narrowing because empirical treatment is frequently initiated in diagnostically uncertain circumstances.

The most useful interventions were prospective review, diagnostic stewardship, pneumonia pathways, urinary-culture stewardship, intravenous-to-oral conversion, and discharge-duration review.

A recent observational study of patients hospitalised with community-onset sepsis found that broad-spectrum de-escalation by day four was associated with similar safety outcomes, fewer antibiotic days, and shorter hospitalisation, although residual confounding remained possible.

Medical stewardship should include review of the complete treatment episode, because excessive duration often extends into the discharge prescription.

14. Surgery

Surgical stewardship begins before incision through appropriate prophylaxis selection, timing, dose, and redosing. Prophylaxis should then be discontinued after the recommended period.

Prolonged prophylaxis is not equivalent to treatment and does not compensate for inadequate infection prevention.

When postoperative infection is suspected, de-escalation depends on source control. Persistent fever or inflammatory-marker elevation may indicate an undrained collection, anastomotic leak, devitalised tissue, or another complication. Antimicrobials should be narrowed according to operative cultures when these specimens are reliable. Duration should be limited after adequate control of the infectious source.

15. Intensive Care

Intensive care presents the greatest tension between early broad therapy and later de-escalation. Critically ill patients may deteriorate rapidly when initial treatment is inactive, but they also accumulate substantial antimicrobial exposure.

Daily reassessment is preferable to a single one-time review because haemodynamic status, organ function, microbiology, and source-control information can change rapidly.

De-escalation should be considered after clinical stabilisation and microbiological clarification. Nevertheless, the evidence does not support obligatory spectrum narrowing in every patient.

Biomarker-guided discontinuation has stronger randomised evidence than formal spectrum de-escalation. The major procalcitonin trials reduced exposure without an identified increase in mortality.

16. Oncology and Haematology

Prompt empirical antipseudomonal treatment remains essential in high-risk febrile neutropenia. Stewardship should not delay initial therapy.

The primary opportunities are reassessment of empirical vancomycin, discontinuation of unnecessary combination therapy, narrowing after culture results, and earlier cessation in selected stable patients.

Vancomycin should be continued only when clinical or microbiological findings support resistant Gram-positive infection, catheter infection, pneumonia, skin infection, or haemodynamic instability.

Controlled evidence supports earlier discontinuation in selected stable patients without documented infection, but these findings should not be applied to patients with shock, pneumonia, bloodstream infection, or an uncontrolled focus.

17. Clinical Outcomes and Safety

Most studies reported no increase in mortality, treatment failure, recurrence, or readmission after stewardship-supported discontinuation or de-escalation.

However, safety depended on patient selection and diagnostic quality. Studies frequently excluded unstable patients or applied explicit criteria before treatment modification.

Mortality alone is insufficient for safety assessment. Programmes should also monitor recurrence, escalation, superinfection, fungal infection, adverse drug events, readmission, and time to appropriate therapy.

Observational associations between de-escalation and lower mortality should be interpreted cautiously because clinical improvement makes both de-escalation and survival more likely.

18. Antimicrobial Resistance and Ecological Outcomes

De-escalation reduces broad-spectrum exposure and may reduce selection pressure, but effects on resistance are difficult to measure and attribute.

Resistance is influenced by hospital-wide and community antimicrobial use, patient transfer, colonisation pressure, infection-prevention practice, environmental reservoirs, and outbreak strains.

Short-term prescribing improvement should therefore not be expected to produce immediate hospital-wide susceptibility changes.

The AWaRe system supports monitoring and benchmarking of Access, Watch, and Reserve antibiotic use and can complement patient-level de-escalation measures.

19. Cross-Specialty De-escalation Framework

Table 2. Specialty-specific transition from empirical treatment to definitive therapy

Specialty	Typical empirical approach	Principal reassessment question	Common de-escalation action	Main safety safeguard
General medicine	Broad treatment for uncertain pneumonia, urinary infection, sepsis, or fever	Is bacterial infection still likely?	Discontinue, narrow, convert to oral therapy, shorten duration	Clinical response and diagnostic reassessment
Surgery	Perioperative prophylaxis or broad treatment of postoperative infection	Is this prophylaxis or established infection, and is source control adequate?	Stop prophylaxis, narrow after cultures, limit duration after source control	Adequate peri-incisional coverage and source control
Intensive care	Immediate broad-spectrum treatment for severe sepsis or shock	Is the patient stable, is therapy active, and are microbiological data reliable?	Remove combination therapy, narrow spectrum, biomarker-supported stopping	Timely active therapy, adequate dose, daily review
Oncology/haematology	Prompt antipseudomonal therapy for febrile neutropenia	Is documented infection, instability, or an indication for additional coverage?	Discontinue combination therapy, selected early cessation	vancomycin, stability criteria and specialist monitoring

20. Organisational Requirements

Safe de-escalation requires leadership support, accountable programme ownership, infectious-diseases expertise, clinical pharmacy, microbiology, nursing participation, data systems, and specialty engagement.

The microbiology laboratory must provide timely results, guidance on specimen quality, selective susceptibility reporting, and interpretation of resistance mechanisms.

Pharmacists contribute to dose optimisation, drug-interaction review, therapeutic drug monitoring, intravenous-to-oral conversion, and documentation of duration.

Electronic systems can support time-outs, positive-culture alerts, review dates, dose warnings, and discharge reconciliation. Excessive alerts should be avoided because alert fatigue may reduce attention to important recommendations.

21. Integrated Empirical-to-De-escalation Pathway

The evidence supports a six-stage clinical pathway. The first stage is appropriate empirical initiation based on infection probability, severity, source, patient risk, and local epidemiology. The second stage is collection of reliable diagnostic specimens and urgent source-control assessment.

The third stage is structured review within 24–72 hours using clinical response, cultures, susceptibility results, imaging, biomarkers, and organ function. The fourth stage is selection of the definitive action: discontinue, narrow, remove combination therapy, broaden, adjust dose, convert route, or pursue additional diagnostics or source control.

The fifth stage is documentation of total duration, monitoring, and discharge treatment. The final stage is organisational feedback using antimicrobial exposure, appropriateness, treatment failure, toxicity, recurrence, readmission, mortality, *C. difficile*, and resistance.

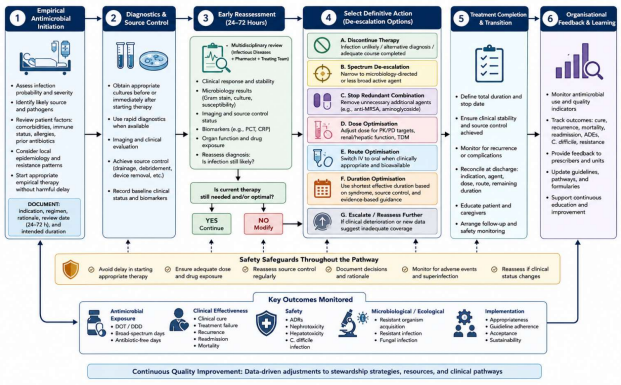

Figure 2. Integrated pathway from empirical antimicrobial initiation to diagnostic reassessment, discontinuation,

spectrum de-escalation, dose and route optimisation, treatment completion, and organisational feedback.

22. Discussion

This systematic review found that the transition from empirical antimicrobial treatment to definitive therapy is one of the most important functions of hospital stewardship. Broad empirical treatment may be appropriate at presentation, particularly in severe infection, but continuation without reassessment exposes patients to avoidable harm.

The evidence was strongest for structured review, complete discontinuation when infection became unlikely, treatment-duration reduction, and procalcitonin-supported cessation. Evidence for obligatory spectrum de-escalation was less definitive.

The randomised severe-sepsis trial showed that formal de-escalation was feasible but did not produce a simple reduction in total antibiotic exposure and raised concern regarding superinfection. This finding does not indicate that de-escalation should be abandoned. It demonstrates that spectrum narrowing should be clinically governed rather than treated as an automatic performance requirement.

Prospective audit and feedback was effective across specialties because it connected stewardship decisions to actual patient information. Rapid diagnostics added value when linked to immediate clinical interpretation.

The meaning of de-escalation differed among specialties. In medicine, complete discontinuation was often the most important action. In surgery, stopping prophylaxis and addressing source control were central. In intensive care, de-escalation required stability, reliable sampling, and adequate dosing. In oncology, treatment modification required explicit risk criteria and close monitoring.

The review also demonstrates that de-escalation includes more than changing from a broad drug to a narrower drug. Removal of redundant combination therapy, intravenous-to-oral conversion, duration reduction, and complete discontinuation may produce equal or greater clinical benefit.

22.1 De-escalation Is Not Undertreatment

Appropriate de-escalation preserves active treatment. It does not mean choosing an inadequate agent, lowering the dose without justification, or stopping treatment despite uncontrolled infection.

Stewardship teams should measure delays in appropriate therapy and inadequate dosing as potential failures alongside excessive use.

22.2 Clinical Improvement and Confounding

Observational studies frequently report better outcomes in de-escalated patients. These findings may be partly explained by clinical improvement because stable patients with reliable cultures are more likely to undergo narrowing.

Randomised and carefully adjusted studies are therefore required to determine the independent effect of de-escalation.

22.3 Microbiology as a Prerequisite

Culture-directed de-escalation cannot be achieved reliably without appropriate specimens and timely reporting. Diagnostic stewardship is therefore inseparable from antimicrobial stewardship.

22.4 Discharge as the Final De-escalation Opportunity

Patients may receive an unnecessarily long or broad discharge prescription despite appropriate inpatient review. Total inpatient days should be counted, and the final diagnosis, agent, route, and remaining duration should be reconciled before discharge.

23. Strengths

This review examined the full pathway from empirical initiation to definitive therapy rather than evaluating antimicrobial consumption alone.

It distinguished complete discontinuation, spectrum narrowing, removal of combination therapy, dose optimisation, route conversion, and duration reduction.

It also compared the clinical meaning of de-escalation across four major hospital specialties and considered prescribing outcomes alongside patient safety and ecological effects.

24. Limitations

The review was not prospectively registered in PROSPERO, and no public protocol was deposited.

Substantial heterogeneity in de-escalation definitions, timing, specialties, infection syndromes, antimicrobial regimens, and outcome measures prevented meta-analysis.

Many observational studies were vulnerable to confounding by clinical improvement and immortal-time bias.

Adverse events, superinfection, recurrence, and post-discharge outcomes were reported inconsistently.

Resistance outcomes frequently had insufficient follow-up.

Some interventions included diagnostics, infection prevention, and broader quality-improvement measures, making the independent effect of de-escalation difficult to isolate.

English-language restriction may have excluded relevant studies.

25. Recommendations for Hospital Practice

Hospitals should preserve prompt empirical treatment for severe infection while requiring reassessment within 24–72 hours. Indication, empirical rationale, review date, and intended duration should be documented.

Diagnostic specimens should be obtained before treatment whenever this does not create harmful delay. Rapid diagnostic results should be linked to immediate stewardship interpretation.

De-escalation should be considered when the patient is clinically stable, the infection diagnosis has been reassessed, microbiological data are reliable, source control is adequate, and the definitive regimen provides appropriate exposure.

Complete discontinuation should be prioritised when infection becomes unlikely. Redundant combination therapy should be stopped promptly. Intravenous treatment should be converted to oral therapy when appropriate.

Specialty-specific pathways should define safety criteria for surgery, intensive care, and oncology. Programmes should measure clinical outcomes alongside antimicrobial exposure.

26. Future Research

Future research should standardise definitions of spectrum de-escalation, discontinuation, and combination-therapy reduction.

Randomised or target-trial-emulation studies are required to reduce confounding by clinical improvement.

Studies should report time to appropriate empirical treatment, total antimicrobial exposure, spectrum, dose adequacy, treatment failure, recurrence, superinfection, fungal infection, readmission, mortality, and resistance.

Further research is needed on rapid diagnostics, artificial-intelligence-supported review, antifungal de-escalation, discharge stewardship, and implementation in resource-limited hospitals.

27. Conclusions

The movement from empirical antimicrobial therapy to definitive, optimised treatment is a central responsibility of hospital stewardship.

Broad empirical therapy may be necessary at the onset of severe infection, but it should not continue without structured reassessment. Clinical response, microbiology, imaging, biomarkers, source control, organ function, and pharmacological exposure should determine the next treatment decision.

The strongest evidence supports timely review, discontinuation when infection is unlikely, removal of redundant therapy, shorter evidence-based durations, and biomarker-supported stopping in selected patients.

Spectrum de-escalation is generally feasible and may reduce broad-spectrum exposure, but it should not be imposed automatically. Safety depends on clinical stability, reliable diagnostics, adequate source control, and an effective definitive regimen.

A successful programme links empirical prescribing with reassessment, optimisation, treatment completion, outcome measurement, and continuous organisational learning.

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