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# A De-escalation Clock for Antibiotics Would Connect Diagnostic Evidence, Host Trajectory, Spectrum, Route, and Duration in a Single Rational-Use Decision

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## ABSTRACT

Antibiotic reassessment is often organized around fixed review points, yet the information needed to modify treatment rarely matures simultaneously. Microbiological evidence may justify spectrum narrowing while the patient still requires intravenous therapy; clinical recovery may permit oral treatment while uncertainty about total duration remains; conversely, negative cultures may provide little reassurance when the host trajectory remains concerning. This For Debate article argues that antibiotic de-escalation is better understood as a set of time-linked but partly independent reassessment processes. Diagnostic evidence, host trajectory, spectrum, route, dose or exposure, and duration should each be reconsidered whenever their relevant evidence changes, without assuming that improvement in one dimension automatically justifies movement in another. The proposed "clock" is therefore not a universal timetable. It is a way to make asynchronous treatment decisions explicit while preserving infection site, pathogen, source control, immune status, severity, pharmacokinetics and pharmacodynamics as determinants of when each modification becomes defensible.

**Keywords:** Antibiotic de-escalation, Antimicrobial stewardship, Diagnostic reassessment, Intravenous-to-oral switch, Treatment duration, Pharmacokinetics

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## Introduction

Antibiotic prescribing is already understood as a sequence of decisions rather than a single act at treatment initiation. The "4 Moments of Antibiotic Decision Making" formalized recurrent questions about whether infection is present, whether cultures and empirical therapy are appropriate, whether therapy can be stopped or narrowed, and what duration is required [1]. This approach helped move stewardship away from a purely retrospective assessment of whether an initial prescription was guideline-concordant. Yet recurrent review does not by itself establish how different components of therapy should be reconsidered when new information arrives at different rates.

That distinction matters because antibiotic de-escalation is not one reproducible intervention. Definitions have included discontinuation of unnecessary agents, narrowing of spectrum, withdrawal of combination therapy, substitution of a drug with lower ecological impact, or other reductions in antimicrobial intensity [2]. These actions can have different prerequisites and different consequences. A microbiological result may justify removal of anti-MRSA coverage without resolving whether the remaining agent should be given intravenously or orally. Clinical recovery may justify route change but provide little information about whether drug exposure is adequate in a critically ill patient. Source control may transform the evidence supporting treatment duration without

changing susceptibility information. Treating all of these events as a binary state of "de-escalated" or "not de-escalated" obscures which decision actually changed and why.

Sepsis guidance already encourages repeated assessment of antimicrobial therapy and supports de-escalation when evolving clinical and microbiological information permits it [3]. The remaining problem is therefore not whether reassessment should occur. It is whether the reassessment process should explicitly recognize that its component decisions have different evidentiary clocks. The useful unit of analysis may be less "Were antibiotics reviewed today?" than "Which treatment dimensions have acquired enough new evidence to justify a change, and which remain unresolved?"

A de-escalation clock, in this sense, would not prescribe a universal hour for action. It would make visible several concurrent reassessment processes whose movement depends on infection site, organism, susceptibility data, source control, host physiology, immune status, clinical trajectory, drug pharmacology and the consequences of treatment failure. Its central proposition is deliberately limited: rational antibiotic use may improve when diagnostic certainty, host response, spectrum, route, exposure and duration are assessed as related but non-identical states. The proposition should fail if these states prove sufficiently synchronized that separate tracking adds no useful information, or if explicit tracking changes neither antimicrobial exposure nor clinical decisions.

*Evidence arrives on different clocks*

Rapid diagnostics illustrate why the timing of information cannot be equated with the timing of a defensible treatment change. In bloodstream infection, the strongest evidence for rapid diagnostic testing is not simply that results become available earlier. A systematic review and network meta-analysis found that rapid diagnostic tests produced greater clinical value when coupled with antimicrobial stewardship activity, including faster optimization of therapy and improved outcomes in some comparisons [4]. The implication is important for temporal reassessment: an earlier test result advances the diagnostic-information state, but treatment moves only when that result is interpreted, judged clinically credible and translated into an actionable prescription.

The distinction becomes clearer when rapid testing does not materially shorten antibiotic use. In hospitalized community-acquired pneumonia, multiplex real-time PCR applied to non-invasive respiratory samples did not produce a statistically significant reduction in antibiotic duration in the randomized trial despite providing additional diagnostic information [5]. This is not evidence that molecular diagnostics are unhelpful. It shows that a faster or richer diagnostic signal can arrive without producing a corresponding movement in antibiotic exposure. Diagnostic evidence therefore has an acquisition time and an action time, and the two need not coincide.

A pragmatic randomized study of a multiplex pneumonia panel similarly reinforces the dependence of diagnostic action on clinical context [6]. A molecular platform may shorten the interval to organism or resistance information, but treatment modification still depends on specimen quality, the probability that a detected organism is clinically causal, the availability of an appropriate narrower agent, the patient's severity and the prescribing response to the result. A de-escalation process that records only when the test became positive or negative loses the more consequential question of when the result became sufficient to alter therapy.

Decision-support interventions show that treatment action itself can be accelerated when the relevant choice is made explicit. In the INSPIRE trial, stewardship prompts embedded in pneumonia prescribing reduced unnecessary extended-spectrum antibiotic use [7]. The prompt did not create new microbiology. It changed how available clinical information was converted into a spectrum decision. This is a different intervention from diagnostic acceleration and should be represented as such.

The same point is visible in the multicentre randomized trial of an opt-out protocol for patients with suspected sepsis [8]. The intervention used a detailed safety assessment before clinicians were prompted to discontinue antibiotics. Antibiotic continuation was reduced, yet only a small proportion of screened patients satisfied the eligibility process for randomization. That finding is central to any time-anchored approach. A calendar review point can occur for everyone, while true stopping readiness may occur only for patients whose host state, microbiology and competing risks jointly support it. A clock that equates "time for review" with "time to stop" would erase precisely the clinical distinctions that made the intervention safe enough to test.

Real-world de-escalation adds another layer of heterogeneity. In a large US cohort of patients treated empirically for suspected sepsis with anti-MRSA and antipseudomonal agents, de-escalation by day 4 occurred in fewer than one-third of cases and varied substantially across hospitals [9]. Narrowing and complete cessation were themselves different events. De-escalation was associated with microbiological and clinical features, including

information about resistant organisms and illness trajectory, illustrating that the practical probability of change is conditioned by what has become known by that time. Observational associations with outcomes should not be converted into causal claims, but the variation itself argues against assuming a uniform synchronized transition.

Culture-negative serious infection is a particularly strong stress test. In a multicentre cohort examining early discontinuation after initially suspected serious infection with negative cultures, the apparent safety of stopping at 3–4 days depended on case definition and analytic approach [10]. Negative cultures provided no microbiological confirmation but did not eliminate uncertainty about infection. A prospective nationwide analysis of sepsis further showed that culture-negative and culture-positive disease can differ in presentation and outcome while both remain clinically important sepsis states [11]. The absence of microbiological confirmation is therefore not equivalent to the disappearance of an antibiotic indication.

These findings support a distinction between diagnostic certainty and diagnostic closure. Diagnostic certainty should be treated as decision-specific evidence sufficient to materially alter the probability or identity of infection for the antibiotic decision under consideration. A negative blood culture may be sufficient to remove one resistant-pathogen concern while remaining insufficient to stop all therapy. A respiratory molecular result may support narrowing while leaving uncertainty about duration. Host deterioration may appropriately prevent movement even when microbiological evidence becomes more reassuring. Evidence thus arrives on several timelines, and disagreement between those timelines is not necessarily a failure of stewardship; it may be the correct representation of unresolved clinical risk.

*Diagnostic revision and spectrum de-escalation*

Spectrum is the antibiotic dimension most directly linked to new microbiological evidence, but even here narrowing should not be treated as a mechanical response to a laboratory result. The SIMPLIFY randomized trial tested structured de-escalation from antipseudomonal β-lactams in bloodstream infection due to Enterobacterales and provides direct evidence that susceptibility-informed narrowing can be undertaken in appropriately selected patients [12]. Its relevance is not that every patient should be narrowed at a common elapsed time. It is that a particular treatment dimension—spectrum—can become change-ready once organism identification, susceptibility information and clinical eligibility align.

This creates a useful separation between the timing of diagnostic revision and the timing of spectrum modification. Diagnostic revision begins as soon as new information changes the probability of candidate infections or pathogens. Spectrum movement occurs only when that revised information supports a safer or more targeted antimicrobial choice. The two processes are linked, but they are not identical. A susceptibility report may strongly support removal of antipseudomonal activity while providing no reason to alter route. Conversely, a patient whose cultures remain non-diagnostic may still reach a point at which empirical MRSA coverage is no longer justified because clinical, epidemiological and testing evidence collectively lower the probability of MRSA disease.

Host trajectory modifies this translation. Persistent shock, uncontrolled infection, worsening organ dysfunction or failure to achieve source control can legitimately slow a spectrum or cessation decision even when microbiological information becomes more reassuring. The safety-screen logic used in structured discontinuation studies reflects this principle [8]. The clock therefore needs a host-response state that can interact with diagnostic evidence without being absorbed into it. Clinical improvement is not a microbiological test; microbiological negativity is not clinical recovery.

This distinction is also relevant to how de-escalation should be measured. A patient whose vancomycin is stopped while broad Gram-negative therapy continues has undergone one clinically meaningful de-escalation event. A patient whose antipseudomonal β-lactam is replaced with a narrower active agent has undergone another. Complete antibiotic cessation is a third event. Combining them into a single binary endpoint can be appropriate for some implementation questions, but it weakens the ability to identify which evidence actually changed practice. For a time-linked reassessment model, the more informative question is whether a specific dimension moved when its supporting evidence became adequate, remained static because important evidence was missing, or moved despite unresolved risk.

The practical consequence is that diagnostic stewardship and antibiotic stewardship should be connected without assuming a one-to-one rule between test and prescription. The diagnostic hand can advance when etiological information improves; the spectrum hand advances when that information becomes therapeutically actionable;

the host hand may support or constrain the transition. When these states are discordant, forcing simultaneous movement can be as irrational as failing to reconsider therapy at all.

*Route eligibility and exposure adequacy*

Intravenous-to-oral switch provides the clearest example of why one antibiotic clock cannot be reduced to elapsed time. A systematic rapid review of adult IV-to-oral switch criteria identified a broad set of requirements spanning timing of review, clinical signs and symptoms, infection markers, enteral absorption and infection-specific exclusions [13]. Review at approximately 48–72 hours is common in policy and stewardship practice, but the evidence does not support treating that interval as a universal mandate. It is better understood as an opportunity to ask whether route eligibility has emerged.

Route eligibility has a pharmacological component. Antibiotics with adequate oral bioavailability and predictable exposure can sometimes achieve therapeutic concentrations without intravenous administration, and clinical pharmacology supports earlier oral conversion for appropriate drug–infection combinations [14]. Yet bioavailability alone is not sufficient. Gastrointestinal function, dose, organism susceptibility, site penetration, adherence feasibility and the consequences of underexposure all remain relevant. The route question is therefore connected to exposure but cannot substitute for it.

Observational evidence in community-acquired pneumonia illustrates the practical feasibility of early oral switch. In a large multicentre cohort, early conversion from intravenous to oral therapy was associated with lower intravenous antibiotic use and favorable utilization outcomes without an obvious safety penalty [15]. The association is clinically useful but should not be mistaken for randomized proof that every stable patient should switch at the same point. Patients selected for early oral treatment may differ systematically from those who remain on intravenous therapy.

Randomized evidence across other infections makes the infection-specific nature of route readiness even more apparent. Oral step-down has been tested in selected Gram-negative bacteraemia, low-risk *Staphylococcus aureus* bloodstream infection and bone and joint infection [16–18]. In Gram-negative bacteraemia, eligibility required initial active intravenous treatment, clinical stability and control of the infection source. The SABATO trial addressed a deliberately restricted low-risk *S. aureus* population, not complicated bloodstream infection. In bone and joint infection, oral therapy could replace prolonged intravenous treatment while the overall therapeutic course continued. These trials support oral treatment in carefully defined settings, but their different eligibility rules are evidence against a universal route-switch clock.

Partial oral treatment of stable left-sided infective endocarditis provides an even stronger demonstration that route and duration are separable [19]. Selected patients could change administration route after initial stabilization while still requiring completion of a prolonged antimicrobial course. A system that interprets oral conversion as equivalent to “antibiotic de-escalation completed” would miss the continued importance of treatment duration, organism, anatomic infection and follow-up.

Route also has to be distinguished from dose and exposure. Critically ill patients can have profound pharmacokinetic variability caused by altered volume of distribution, changing renal clearance, organ support and other physiological changes. Model-informed precision dosing has therefore been proposed as a means of increasing target attainment, but randomized evaluation has not shown that pharmacometric individualization automatically translates into improvement in every clinical or treatment endpoint [20]. This result is important because the logic of a de-escalation clock must not treat technical optimization as proof of clinical benefit.

Therapeutic drug monitoring offers another way to reassess exposure. For β-lactam antibiotics in critical illness, concentration measurements may reveal underexposure or excessive exposure that is poorly predicted by conventional dosing assumptions [21]. Exposure can consequently require upward adjustment, downward adjustment or no change even while other dimensions are moving toward less intensive therapy. A patient may be microbiologically ready for a narrower agent but physiologically require careful dose optimization. The direction of rational treatment modification is therefore not always “less” across every hand.

The BLING III randomized trial reinforces that pharmacological plausibility and clinical outcome certainty should remain separate [22]. Continuous infusion of piperacillin–tazobactam or meropenem was designed to improve β-lactam exposure in critically ill patients with sepsis, yet the primary 90-day mortality endpoint was not significantly reduced compared with intermittent infusion, despite differences in some secondary outcomes. This

does not invalidate PK/PD principles. It demonstrates that improving the probability of pharmacological target attainment is not identical to proving a patient-level survival benefit.

Exposure adequacy should therefore be treated as its own reassessment state. It asks whether the selected drug, dose and delivery strategy are plausibly achieving the intended pharmacodynamic exposure in the patient who is being treated now. Route readiness asks whether intravenous administration remains necessary. These questions can influence each other, but neither can replace the other. When route, spectrum and exposure move at different times, asynchronous movement is not inconsistency. It is the expected consequence of asking scientifically different questions.

*Duration follows trajectory, source control, and syndrome*

Duration is the dimension most easily mistaken for a clock because it is expressed directly in days. Yet elapsed time is only the visible surface of the decision. Randomized trials in uncomplicated Gram-negative bloodstream infection have shown that seven-day courses can perform comparably to fourteen-day courses when patients are clinically stable and the infection is adequately controlled [23–25]. The practical lesson is not that the seventh day has universal biological significance. It is that, under defined conditions, evidence accumulated by that point can make further exposure unnecessary.

The BALANCE trial substantially strengthened this argument by showing that seven days was non-inferior to fourteen days for mortality in a broad population with bloodstream infection [26]. Its scale makes shorter treatment increasingly difficult to regard as an exceptional strategy, but its exclusions remain clinically decisive. Patients with conditions requiring prolonged therapy, *Staphylococcus aureus* bacteraemia and important forms of severe immunosuppression were not simply interchangeable with the main trial population. A shorter default therefore becomes defensible only when the infection resembles the population in which the default was tested.

Host trajectory can also contribute to stopping decisions, but the signal cannot be represented as a generic improvement marker. In ADAPT-Sepsis, procalcitonin-guided management shortened antibiotic treatment, whereas the corresponding C-reactive-protein strategy did not produce the same result [27]. Two biomarkers associated with inflammatory state therefore generated different treatment effects when operationalized as stopping tools. A reassessment clock should preserve that difference rather than placing “biomarkers improving” into one undifferentiated host-response category.

Aggregate evidence supports the broader proposition that biomarker-guided discontinuation can reduce antibiotic exposure in critically ill patients, while also showing substantial variation in protocols and certainty across outcomes [28]. This matters because a clock that displays host trajectory should not imply that a single laboratory threshold defines stop readiness. Biomarkers are observations within a clinical trajectory; they do not replace assessment of source control, organ dysfunction, infection site or the consequences of relapse.

Very early discontinuation provides the most demanding test of this principle. In patients admitted with suspected pneumonia but preserved oxygenation, ultra-short antibiotic exposure was associated with similar measured outcomes to longer treatment in a propensity-matched observational analysis [29]. Such findings can identify a population in whom the bacterial-infection hypothesis deserves rapid reconsideration. They cannot establish preserved oxygenation as a stand-alone stopping rule. The decision remains conditional on the total diagnostic and clinical picture.

The accumulated randomized evidence for Gram-negative bloodstream infection now makes seven-day treatment a credible default for many patients with adequate source control and uncomplicated disease [30]. This is an important change in the stewardship baseline. The default, however, remains an evidence-defined default rather than a universal duration. Its validity weakens as infection anatomy, immune status, source control, microbiology or clinical response diverge from the populations studied.

Duration therefore advances differently from spectrum and route. Spectrum may narrow as soon as reliable susceptibility information arrives. Route may change once the patient is stable and an appropriate oral regimen can provide sufficient exposure. Duration can remain unresolved until the clinician has enough information about trajectory, source control and syndrome-specific relapse risk. These differences can be compressed into one comparison only if the evidence required for each movement remains visible.

The clinically relevant distinction is summarized below: the same elapsed time can justify movement in one dimension while leaving another unchanged.

**Table 1.** Evidence conditions that can make individual antibiotic decisions change-ready at different times

| Reassessment dimension | New information that can move the decision | What may change when evidence becomes sufficient | What can legitimately remain unchanged | Why elapsed time alone is insufficient |
|---|---|---|---|---|
| **Diagnostic status** | Organism identification, susceptibility information, molecular results, repeated negative microbiology, revised syndrome probability, source findings | Working diagnosis; probability that antibacterial treatment is still required | Spectrum, route or duration if residual clinical uncertainty remains | Tests become available at different times and differ in actionability |
| **Spectrum** | Susceptibility pattern, resistant-pathogen exclusion, microbiological clarification, improving or worsening host state | Removal of unnecessary agents; narrower active therapy | Route, dose or total duration | Narrowing depends on active alternatives and clinical safety, not simply days of therapy |
| **Route** | Clinical stability, functioning enteral route, oral bioavailability, infection-specific eligibility, feasible oral regimen | Intravenous-to-oral switch | Spectrum and remaining duration | Different infections permit oral treatment under different stabilization requirements |
| **Dose/exposure** | Renal clearance, organ support, measured concentrations, organism susceptibility, changing pharmacokinetics | Dose, interval, infusion strategy or monitoring intensity | Route or duration | Critical illness can change exposure faster than the infection indication changes |
| **Duration** | Clinical trajectory, source control, syndrome-specific evidence, relapse risk, selected biomarker trends | Discontinuation or definition of a shorter remaining course | Route or spectrum if those decisions were already settled | Evidence supporting treatment completion is strongly population- and syndrome-dependent |

*Clinical exceptions and tests of the asynchronous proposition*

The proposed clock becomes clinically meaningful only if it survives the conditions in which conventional de-escalation assumptions are least reliable. Immunocompromise is one such condition, but even here the correct response is not simply "treat longer." In the How Long trial, patients with haematological malignancies and high-risk febrile neutropenia were randomized to a clinically driven strategy for discontinuing empirical antibiotics rather than continuation until neutrophil recovery [31]. The study demonstrates that a traditional host marker can sometimes be decoupled from duration. It does not establish that immunocompromise is irrelevant. Instead, it shows that the identity of the decisive host signal may differ by syndrome.

A second exception is unresolved or uncontrolled infection anatomy. Short-course bloodstream-infection trials generally become less applicable when source control is absent, when a deep focus requires prolonged treatment, or when endovascular or central nervous system infection changes the consequences of failure. Under these conditions, spectrum or route might still change while duration remains fixed by the underlying infection. The hands separate because the mechanisms governing them are different.

*Staphylococcus aureus* bacteraemia makes the same point from the opposite direction. Carefully selected low-risk patients can sometimes undergo oral switch, but the existence of that evidence should not collapse complicated bacteraemia, endocarditis and metastatic infection into the same route decision. A route hand may advance in a low-risk phenotype while the same hand remains deliberately constrained in a patient whose anatomic or microbiological risk is different.

Culture-negative sepsis illustrates diagnostic–host discordance. Microbiological uncertainty can persist while the patient improves, or cultures can remain negative while physiological deterioration sustains a high probability of serious infection. If a clock forced the diagnostic and host states to move together, either unnecessary treatment would continue in recovering patients or therapy could be stopped prematurely in unstable patients. Discordance is therefore information, not noise.

Critical illness creates a further exception because de-escalation toward less intensive therapy can coexist with a need for more intensive exposure management. A narrower drug may require dose escalation or therapeutic

monitoring when renal clearance is augmented. Conversely, changing kidney function can require dose reduction even if spectrum, route and duration remain unchanged. Pharmacological intensity and antimicrobial breadth are not synonyms.

The opposite edge case is a low-risk phenotype in which the probability of bacterial disease falls rapidly. Preserved oxygenation in suspected pneumonia may contribute to a decision to reassess very early, but it cannot operate as an isolated stopping command. It becomes useful only when integrated with the diagnostic picture and host trajectory. This is precisely why the clock must show separate hands rather than a sequence of automatic gates.

These exceptions define the principal failure modes of synchronized de-escalation.

**Table 2.** Clinical configurations in which synchronized de-escalation assumptions can fail

| Clinical configuration | Why a standard synchronized assumption fails | Reassessment dimension most constrained or decoupled | Evidence that becomes especially important | Error produced by forcing simultaneous movement |
|---|---|---|---|---|
| **Culture-negative sepsis with ongoing instability** | Negative microbiology does not eliminate serious infection | Diagnostic status versus host trajectory | Serial physiology, source assessment, alternative diagnoses, repeated microbiology | Premature cessation because "cultures are negative" |
| **Low-risk *S. aureus* bloodstream infection** | Route evidence applies only after careful exclusion of complicated disease | Route | Metastatic focus assessment, endovascular risk, stability, oral-regimen suitability | Generalizing oral-switch evidence to high-risk bacteraemia |
| **Uncontrolled source, endovascular infection or deep focus** | Duration remains determined by infection anatomy even when spectrum can narrow | Duration | Source control, anatomic diagnosis, microbiological clearance | Shortening treatment merely because the patient initially improves |
| **Severe immunocompromise or febrile neutropenia** | Traditional host markers may not map directly to required empirical duration | Host trajectory versus duration | Clinical recovery, documented infection, immune context, syndrome-specific evidence | Either automatic prolonged exposure or unsafe premature discontinuation |
| **Critical illness with unstable pharmacokinetics** | Narrower therapy can still require more intensive exposure management | Dose/exposure | Renal function, organ support, concentrations, susceptibility, PK/PD | Treating "de-escalation" as equivalent to lower dose or lower exposure |
| **Suspected pneumonia with preserved oxygenation and rapid recovery** | Some patients may become plausible candidates for very early discontinuation | Diagnostic status and duration | Oxygenation, alternative diagnosis, clinical trajectory, microbiology | Applying either a fixed long course or an unsupported universal ultra-short course |

**Figure 1** depicts reassessment as a common temporal process while allowing each decision dimension to remain stationary, advance or require renewed scrutiny independently.

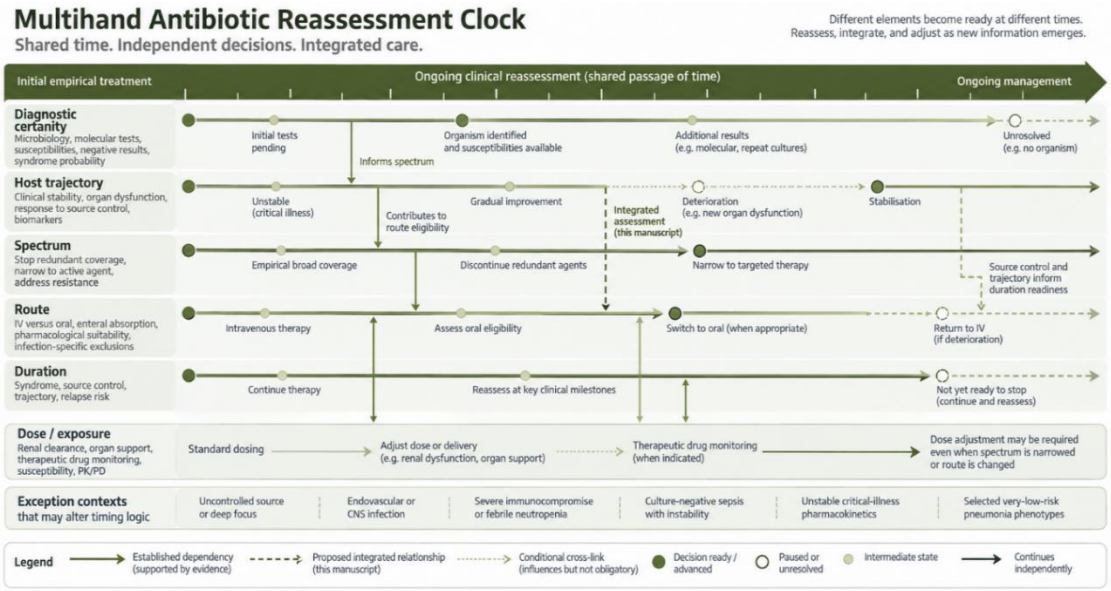


**Figure 1.** Asynchronous antibiotic reassessment across diagnostic, host, spectrum, route and duration decisions

## Conclusion

Antibiotic de-escalation can be organized more coherently when reassessment is treated as time-linked but multidimensional. The evidence supports repeated review and provides increasingly strong foundations for spectrum narrowing, oral conversion, individualized exposure management and shorter treatment in defined populations. What it does not support is a universal hour at which all of these decisions should move together.

The value of a de-escalation clock is therefore not that it tells clinicians when to act. Its value would lie in making explicit which decision has become change-ready, which remains unresolved, and which evidence is preventing or enabling movement. Diagnostic certainty can improve without justifying cessation. Route can change while duration continues. Spectrum can narrow while dose requirements increase. Host recovery can accelerate stopping in one syndrome while anatomy, source control or immune status appropriately delay it in another.

This synthesis remains testable. It should be abandoned if independent tracking of these dimensions does not materially alter prescribing decisions, antimicrobial exposure or safety, or if a simpler synchronized reassessment performs equally well across heterogeneous infections. Until such testing is available, the strongest defensible claim is narrower: antibiotic stewardship should distinguish the time of reassessment from the time at which each specific treatment change becomes justified.

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