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Review

ASP-COMPLEX: redefining antimicrobial stewardship to improve outcomes in high-risk patients with severe infections

PROA-COMPLEX: redefiniendo los programas de optimización del uso de antimicrobianos para mejorar los resultados clínicos en pacientes de alto riesgo con infecciones graves

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Abstract

At a time of great concern regarding trends in morbidity and mortality from infections, and mindful of the limitations of our current approaches to combating them, this document sets out a structured programme of proposals aimed at improving, in the short and medium term, the survival of the most at-risk patients with severe infections. These are complementary proposals which, on the one hand, reinforce already established initiatives and, on the other, introduce some novel aspects to the approach to this complex problem. They focus on accelerating, standardising, and refining the clinical diagnosis of severe

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infection and its microbiological diagnosis and, above all, on improving the effectiveness of antimicrobial treatment, based on its immediate initiation with the most effective treatment available, and with an improved capacity to integrate innovation into all stages and processes. This programme is designed to be implemented within the framework of the Antimicrobial Stewardship Programmes (ASPs) (hence the name ASP-COMPLEX), and requires appropriate dissemination and surveillance policies, alongside a collaborative environment among the multiple stakeholders involved in delivering innovation (experts, ASP teams, healthcare administration, academia, the pharmaceutical industry, etc.).

Keywords: Antimicrobial stewardship programmes. Severe infection. At-risk patients. Antimicrobial resistance. Antimicrobial policy.

Resumen

En un tiempo de gran preocupación por la evolución de la morbimortalidad de las infecciones, y conscientes de las limitaciones de nuestra manera de combatirlas, en este documento planteamos un programa estructurado de propuestas con la intención de mejorar, a corto y medio plazo, la supervivencia de los pacientes más vulnerables con infecciones graves. Se trata de propuestas de carácter complementario, que por un lado refuerzan iniciativas ya consolidadas y por otro replantean algunos aspectos novedosos en el abordaje de este complejo problema. Se centran en acelerar, generalizar y precisar mejor el diagnóstico clínico de la infección grave y su diagnóstico microbiológico y, sobre todo, en mejorar la efectividad del tratamiento antimicrobiano, con base en su inicio inmediato, con la mayor efectividad anticipable disponible, y con una capacidad mejorada para integrar la innovación en todos los pasos y procesos. Es un programa que ha de sustanciarse en el ámbito de los Programas de Optimización de Uso de Antibióticos (PROA) (de ahí el nombre de PROA COMPLEX), y que requiere unas adecuadas políticas de difusión y de vigilancia, además de un contexto de alianzas entre los múltiples agentes implicados en la provisión de innovación (expertos, PROA, administración, academia, industria farmacéutica, etc.).

Palabras clave: Programa de optimización de uso de antibióticos. Infecciones graves. Pacientes de riesgo. Resistencia antimicrobiana. Política de antibióticos.

1. Introduction

The problem

Mortality associated with infections constitutes one of the most significant public health challenges globally. It is estimated that infectious diseases contribute to approximately 20% of global mortality, with particularly high and sustained case-fatality rates in the context of severe infections and sepsis [1]. In recent decades, notable international awareness has developed regarding this problem, accompanied by multiple initiatives aimed at optimising antimicrobial use and curbing the threat of resistance [2-22]. However, despite these efforts, available evidence has not consistently demonstrated a significant reduction in mortality associated with severe infections [23-29]. This apparent mismatch suggests a need to critically review current approaches and explore new conceptual frameworks explicitly oriented towards reducing morbidity and mortality, both at the individual patient level and in terms of global health.

The reasons why we have failed to substantially reduce mortality associated with infections, or to counteract increasingly alarming projections, are complex and multifactorial. Factors certainly include the continuous increase in at-risk patients—who are more prone to infection and to progression to severe disease and death—as well as the complexity of these infections and their clinical management, which diversifies and hinders adherence to standards of care and guidelines. This scenario places increasing pressure on healthcare systems, exposing structural and organisational limitations that directly impact clinical outcomes and threaten the sustainability of the healthcare systems.

Another key factor is the development of antimicrobial resistance (AMR), which is directly linked to antimicrobial exposure and the selective ecological pressure it generates. AMR has substantially increased patient vulnerability, compromised microbiological diagnosis—making diagnostic delay a clear risk factor for mortality—and complicated the therapeutic management of infections due to the limited availability of effective options and higher rates of treatment failure, ultimately leading to a significant increase in morbidity and mortality [23, 25-28, 30].

Our response (The current model)

Status analysis. Although there are many other factors that increase patient vulnerability, complicate clinical management, and compromise outcomes, AMR has emerged as one of the most visible and potentially actionable determinants of this problem. For decades, it has formed the core rationale for antimicrobial

control policies and antimicrobial stewardship programmes (ASPs) [2-4, 7-22, 31].

In practice, and predominantly for more than 30 years, the main objective of many of these programmes has been the containment or reduction of antimicrobial consumption, through initiatives promoting the appropriate, rational, or prudent use of antibiotics. This approach explains why the key data used by ASPs, national plans (such as the PRAN in Spain), the European Centre for Disease Prevention and Control (ECDC), and the World Health Organization Global Action Plan (WHO GAP) are antimicrobial consumption (measured in DDD, DOT, and expenditure) and the rate or trend of infections caused by resistant bacteria.

Consequently, current objectives—formulated in 2018 and projected through to 2030—prioritise a 20% reduction in global antibiotic consumption (27% in the case of the PRAN in Spain [32]) and promote the use of older, narrow-spectrum antimicrobials in at least two out of three prescriptions, according to the WHO Access, Watch and Reserve (AWaRe) classification [15-18]). These efforts aim to achieve a 3%—15% reduction in the incidence of certain severe infections caused by multidrug-resistant (MDR) bacteria by 2030. These are essentially preventive, ecologically driven objectives that seek first to minimise AMR, and subsequently, in the medium to long term, reduce the morbidity and mortality associated with infections.

The overriding concern with the 'ecological preservation' of antimicrobial therapies often leads to restrictive usage policies, particularly regarding innovative products. These are frequently viewed as 'endangered species' that must be protected to maintain their future efficacy [33], enforced through external controls, validations, and rigorous prescribing criteria [34-36]. As a consequence, the needs of current patients with severe infections and high mortality risk—who require the most effective treatments—may be overlooked. To address this, more real-time attention should be devoted to identifying and correcting insufficient or suboptimal treatments, and to reducing the administrative and scientific barriers that limit access to intensified, personalised antibiotic therapies and innovation.

Results. Although these policies have been in place and have enjoyed broad administrative support for over 30 years, recent data show that, between 2018 and 2023, the targets for reducing overall antibiotic consumption, the consumption rate of antibiotics in the Watch and Reserve group, and AMR-associated infections have not been met. On the contrary, the global incidence of these infections has increased significantly—by approximately 40% worldwide [29], with similar trends observed in Europe [37-39] and Spain [40].

The Organisation for Economic Co-operation and Development (OECD) predicts that infections caused by bacteria resistant to 'last-resort antibiotics' will double (with increases ranging from 50% to 300%) between 2005 and 2035 [41-42]. In Africa, mortality attributable to AMR now exceeds the combined death toll of tuberculosis, malaria, and HIV, despite receiving far less attention and investment [43-44].

Similarly, mortality and case-fatality rates for severe infections associated with AMR have shown no improvement [1, 23-27, 45]. Real-world data from Spain [28] place these figures significantly higher than the international estimates, such as those from the WHO, which identify AMR as the leading cause of death by 2050 [10]. Furthermore, robust predictive models suggest that, without a strategic pivot, mortality (attributable and associated) will enter a phase of continuous increase up to 2050 [27].

This scenario has ultimately prompted a reassessment of the problem on the international political agenda. In September 2024, the political declaration of the second UN General Assembly High-Level Meeting on AMR, and in May 2025 at the 78th World Health Assembly, established a clear global commitment to reduce AMR-associated mortality [46-47]. To this end, the 10-20-30 Agenda was finalised. This agenda aims to achieve, by 2030 relative to 2019, a 30% reduction in the inappropriate use of antibiotics in animals, a 20% reduction in humans, and, for the first time, a specific target of a 10% reduction in mortality [44, 46, 47]. Achieving this seems highly unlikely without fundamental conceptual, structural, and cultural changes to our current strategies [27-28].

Conclusion. Consistently available data indicate that our response to this challenge has not delivered the expected outcomes, and that our current model for combating severe infections and AMR has become disconnected from clinical outcomes.

This realisation demands a strategic review to realign our efforts towards improving clinical outcomes and driving down mortality. We require a reframing and reconfiguration of the existing model to generate, complement, and reinforce concrete, operational initiatives that can impact clinical outcomes and improve the real-world prognosis of these infections in the short to medium term.

2. Review and reconfiguration of the diagnosis and treatment of severe infections

To bring about real operational changes in how we approach severe infections and their high associated mortality, it is essential to:

A. Recognise and address the limitations of current antibiotic policy

Conceptual limitations

Current antibiotic policies present at least two significant conceptual issues:

1) **The excess mortality associated with infections is primarily and predominantly due to the problem of AMR.** It is vital to acknowledge that many other factors influence mortality besides resistance—including biological vulnerability, as well as social, structural, and care-delivery factors. These can exert an even greater impact than AMR itself and warrant increased attention [27, 41-43]. This involves better, broader, and earlier recognition of severe infections, their specific aetiology, and their complex physiopathology (resistance, virulence, persistence, etc.), alongside the pursuit of more individualised and effective treatments.

2) **AMR is primarily caused by the excessive and inappropriate use of antimicrobials** [8, 10-12, 16, 18, 22, 32-33, 38, 48-51]. AMR is a biological phenomenon of such complexity [52-55] that relying solely on prudent and appropriate use to control it may prove insufficient. Inappropriate antibiotic use remains a key, modifiable driver of resistance. However, trying to strictly define, validate, standardise, and enforce 'appropriate' or 'rational' antibiotic use is practically unattainable given the immense complexity and variability of managing severe infections in real clinical settings [56-57]. Furthermore, other independent factors influence the development of resistance—including necessary, appropriate exposure to antimicrobials—meaning that even the most perfect prescribing controls would ultimately be insufficient to halt AMR.

   As early as 2008, the Infectious Diseases Society of America (IDSA) noted that: "it is commonly expressed that physician misuse of antibiotics is the cause of antibiotic resistance in microbes, and that if we could only convince physicians to use antibiotics responsibly, we could win the war against microbes. Unfortunately, this belief is a fallacy that reflects an alarming lack of respect for the incredible power of microbes" [58]. We must accept that the true driver of AMR is the extraordinary adaptive capacity of microbes, which has evolved over more than three billion years in a continuous struggle for survival, allowing them to evade virtually any antimicrobial product or strategy through a wide array of mechanisms—often even before direct exposure [58-60].

   Evidence shows that resistance is deeply embedded in the bacterial genome and can emerge and persist independently of antimicrobial exposure [59, 61-66]. This does not only occur randomly or *de novo*; it is often driven by natural exposure to hostile environments and biological compounds (such as host immune responses or natural antimicrobial peptides). Such encounters exert selective pressure that promotes adaptive mechanisms, which can then confer cross-resistance to synthetic antibiotics without any prior exposure [58-59, 61, 67]. Furthermore, resistance genes can disseminate horizontally even in the absence of antibiotic pressure [68-71].

   Moreover, as long as antibiotics remain essential to treat infections, any use of these agents —including appropriate and necessary therapy— will continue to serve as a driver of the development of resistance [59]. This is further complicated by phenomena like 'genetic capitalism' [72], where bacteria already carrying multiple resistance genes acquire and accumulate additional genetic elements. This process frequently occurs in severe clinical settings where complex, appropriate therapies are required, resulting in higher levels of AMR, cross-resistance, co-resistance, and the unmasking of cryptic resistance. These dynamics drive the continuous expansion of the microbial resistome [29, 45, 73], extending far beyond the issue of inappropriate antibiotic use [58-72].

   From this perspective, controlling antibiotic use, while necessary and clinically relevant in many local contexts, is inherently insufficient as a standalone strategy to contain AMR. In a world dominated by microbes with superior evolutionary adaptability, our goal should not be to win an impossible battle (such as eradicating pathogens or achieving a perfect ecological balance via 'appropriate' use), but rather to minimise the negative consequences of their adaptation [59]. As the IDSA succinctly stated: "Here, the resource that must be protected and restored is antibiotic effectiveness" [58].

In practical terms, and to give an example from clinical practice, the focus should be more on the clinical efficacy of antibiotics than on their environmental

impact [59]. It entails focusing more on the 'last-line' antibiotic that was withheld despite being clinically indicated, than on the antibiotic that was unnecessarily prescribed—provided the latter was effective and did not directly cause clinical harm. This perspective should not be interpreted as a dismissal of ecological stewardship principles, but rather as an attempt to dynamically balance individual patient benefit with long-term ecological responsibility in particularly high-risk scenarios. If our approach over the last 75 years has not been sufficiently successful, we must refine it, pursuing continuous improvement to close the gap between human innovation and the evolutionary advantage of the microbial genome [9, 58-59, 74].

Methodological limitations

In their attempt to reduce variability in clinical practice and control costs, our antibiotic policies harbour methodological problems that may hinder, in the clinical setting and in real time, therapeutic precision, individualisation, and the transfer of the benefits of innovation to the patients who need them most. Examples include:

- **Inefficiency of academic training.** Training clinicians to manage complex infections effectively is challenging [75,76]. Traditional educational programmes are voluntary, highly dependent on teaching quality, often lack clinical context, and tend to oversimplify management. They typically focus on protocolisation, reducing clinical variability, preventing AMR, and achieving cost efficiency [8, 16, 18, 22, 32-33, 38, 48-51, 77]. Consequently, the urgent needs of at-risk patients with severe infections are often omitted from this training framework. Digital solutions, advanced software, and artificial intelligence (AI) tools capable of providing structured, real-time clinical decision support systems (CDSS) offer promising ways to overcome these limitations [78].
- **Over-reliance on the highest-level scientific evidence when formulating recommendations, protocols and guidelines.** While evidence-based medicine is fundamental, insisting on the highest-level evidence (such as large meta-analyses) to guide every prescription can result in suboptimal care for the most at-risk patients [16, 18, 33-34, 79-83]. The methodologies used to generate this evidence are often designed for chronic conditions rather than acute, severe infections. As a result, genuine clinical benefits in critical and complex scenarios may not meet standard evidence thresholds and are excluded from clinical guidelines (e.g., non-inferiority studies, which are accessible but provide little impetus for adopting therapeutic innovations) [79-85]. Optimising the management of these infections requires a more adaptive, less dogmatic approach that incorporates diverse evidence sources, including observational and real-world data, structured clinical experience, and expert consensus.
- **Outsourcing of governance and control over prescribing.** Antimicrobial treatments are often subject to strict control by external departments such as pharmacy, microbiology, preventive medicine, infectious diseases committees, ASPs and health administration, which regulate acquisition and dispensing based on centralised therapeutic positioning reports and adherence to rigid guidelines. While these controls aim to prevent AMR and contain costs, they often favour highly restrictive practices for the most innovative and expensive agents. This can introduce delays and inflexibility in patients with severe infections, where early, individualised therapy directly determines prognosis [4, 84-91]. Properly structured stewardship teams should instead facilitate the positioning and delivery of innovative pharmacological, diagnostic, and clinical resources to these critical patients.

Ethical limitations

Protecting and preserving the long-term effectiveness of antibiotics is a core ethical duty towards future patients. However, in severe infections affecting highly vulnerable individuals, a fundamental ethical tension arises between the immediate benefit to the individual and long-term collective responsibility. This conflict cannot be resolved solely through general policies or isolated individual decisions; it requires an integrated approach that balances the specific clinical context with population-level impacts.

The legitimacy of limiting potential benefits for a current patient to preserve future utility depends on clinical severity, diagnostic uncertainty, and the availability of effective therapeutic alternatives. While the future benefits of antibiotic containment may be contingent and dependent on broader scientific progress, they remain a valid consideration within a framework of intergenerational equity. The ethical challenge is therefore to find a dynamic balance that maximises immediate clinical benefit without disproportionately compromising the future sustainability of antimicrobial therapies [87, 92].

Philosophical limitations

The fact that a particular viewpoint has become the 'official view' and remains widely supported for many years does not mean that it is always the most correct or effective solution for complex problems. Self-criticism requires acknowledging that knowledge management is often subject to cognitive biases that

entrench intellectually attractive positions, even when they diverge from real-world outcomes [93].

The primary focus on preventing AMR solely through the 'appropriate use of antibiotics' is a clear example of anchoring heuristic—a cognitive bias whereby we anchor ourselves to a compelling initial solution and limit our search for better alternatives. This anchoring explains why institutions continue to measure antibiotic consumption and resistance rates—which are familiar and relatively easy to track—rather than monitoring real-world clinical outcomes and mortality, which are more complex to capture but represent the ultimate metric [51, 94].

B. Recognise the need to refocus and revisit the current antibiotic policy

The strategy should be focused on an ASP aimed at severe infections in the most at-risk patients and centred on therapeutic effectiveness. ASPs have driven major progress in optimising antimicrobial use and raising awareness of AMR. However, given the limitations outlined above, they have not consistently improved clinical outcomes, which should remain their foremost objective. A strategic adjustment is therefore needed. This does not mean replacing current ASP models, many of which already incorporate several of these principles, but rather expanding stewardship towards a more outcome-oriented and effectiveness-driven framework in selected high-risk scenarios.

This reconfiguration is built upon three primary pillars:

- **Target population:** Focussed on high-risk, at-risk patients with severe infections that are 'difficult to treat'. These are the patients who experience the highest mortality rates and for whom restrictive prescribing policies are often least successful. Although vulnerability to infectious diseases is a very broad, complex and difficult-to-define concept, encompassing genetic, biological, psychological, social, administrative and political factors that are difficult to characterise and apply [27, 95-97], in this document, for operational reasons, we define vulnerability on the basis of clinical and biological criteria that are well-validated in the healthcare setting, with a demonstrated capacity to severely impair the patient's immune response to infection and/or to hinder or delay access to effective treatment, thereby increasing the risk of disease progression and mortality [98-101] (**Figure 1**).

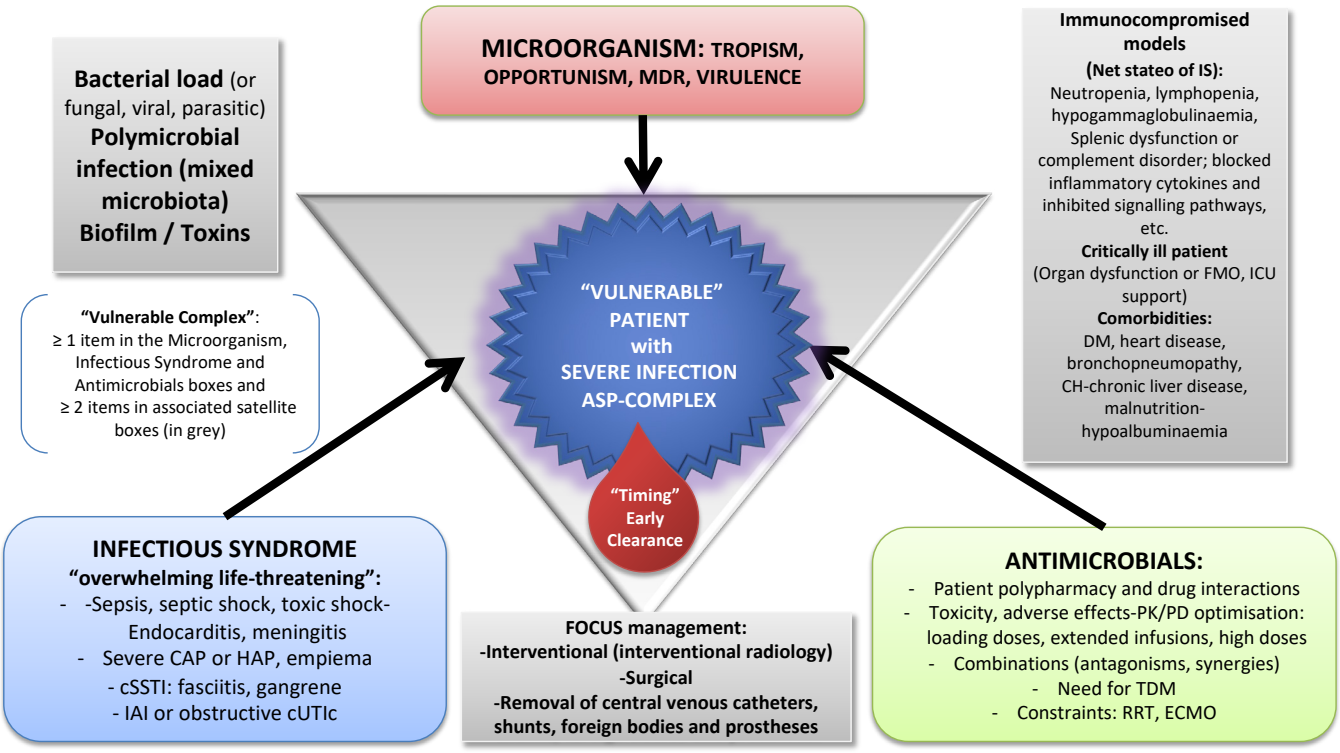

Figure 1. Clinical-biological factors influencing vulnerability to infections

MDR: multidrug resistance; PK/PD: pharmacokinetics/pharmacodynamics; MOF: multiple organ failure; TDM: therapeutic drug monitoring; RRT: Renal replacement therapy; cSSTI: complicated skin and soft tissue infection; cIAI: complicated intra-abdominal infection; CVC: central venous catheter; UC: urinary catheter; IS: immunosuppression; LC: liver cirrhosis; ECMO: Extracorporeal Membrane Oxygenation.

Thus, the main factors contributing to vulnerability would be: a) clinical or pharmacological immunosuppression (of varying intensity depending on aetiology, duration of illness, treatment, net state of immunosuppression, etc.); b) Immune compromise or immune dysfunction occurring in the critically ill patient (due to immunoparalysis associated with the severity of the condition or the imbalance between immune exhaustion and the hyperinflammatory phases of shock), in patients with severe, multiple or decompensated comorbidities (as these significantly reduce 'functional reserve'), or in geriatric frailty [100, 102-106]; c) the presence of prosthetic/invasive devices (which, through biofilm, create 'sanctuaries' that are very difficult for antibiotics to access, and which impair the defensive capacity of the 'invaded' organs); and d) colonisation by AMR-bearing microbes, the risk of which is increased in the conditions described above, but above all in patients with recent (within 6 months) exposure to antimicrobials or to the healthcare system (especially if there are problems with AMR endemicity) [107-112].

Although a precise, validated and reproducible definition of vulnerability was critical to our aims, the fact is that, given the need to protect these patients in the short term, we have adopted a pragmatic definition—setting aside the academic rigour required for research—under which we consider a patient to be vulnerable if they meet any of the criteria listed above. We believe that there remain more issues of sensitivity than of specificity in the operational definition of vulnerability commonly used in clinical practice; therefore, we believe that, rather than hindering its application with proposals for rigid, validated scales or 'scores', it makes sense to liberalise it, in order to facilitate the attribution of vulnerability.

- **Primary objective: To maximise the effectiveness of antimicrobial treatment.** In the context of realigning antibiotic policy with improved clinical outcomes, priority should be given to achieving therapeutic effectiveness, understood as maximising the likelihood of rapid microbial eradication and early clinical control, which have a direct impact on mortality. This is achieved by taking due account of the probable aetiology, the patient's characteristics, the clinical syndrome and the site of infection, as well as the pharmacokinetics/pharmacodynamics (PK/PD) of the antibiotic treatment.

  In practical terms, this implies:

  - Encouraging prescribers to adopt a decisive commitment to providing, for each individual patient, the antibiotic treatment with the highest degree of anticipated effectiveness available. In this challenging prescribing scenario, what is appropriate is what is effective (beyond ecological impact, previous conventions regarding appropriate or adequate therapy, efficacy in the Petri dish, and the recommendations of guidelines).
  - The promotion of initiatives and proposals that facilitate the prescribing of effective treatments. This is the critical point of the entire programme: the conviction—which we share with recent institutional proposals [42, 113-115]—that, in the face of a severe, 'difficult-to-treat' infection in the target population we have defined, decision-making must prioritise immediate clinical effectiveness, whilst always maintaining a dynamic balance with the need to minimise the ecological impact. ASPs and antibiotic policies that place greater emphasis on restrictive programmes for the prevention and reduction of AMR development and costs achieve variable and inconsistent results regarding the evolution of AMR [116] and, above all, regarding the improvement of the most important clinical outcomes [4, 86, 94, 117-119].

  An inevitable consequence of this approach is the need to assess and monitor mortality as the primary indicator of effectiveness in any setting (ASP) treating this type of infection and these 'difficult-to-treat' patients. It is also important to monitor aspects related to morbidity, including complications, sequelae, readmissions, adverse effects, drug interactions, etc.

- **Operational management framework: ASP and the ASP-COMPLEX concept.** We refer to this proposal as 'ASP-COMPLEX' because, although it consists of a set of recommendations aimed at prescribers to facilitate (and restore) therapeutic effectiveness, we understand that they can only be implemented from a multidisciplinary, expert, realistic and adaptable perspective linked to the healthcare administration of ASP's.

  The 'ASP-Complex' approach involves reviewing the clinical care pathway for this type of infection, seeking out and identifying obstacles that may be blocking or slowing down access to the effectiveness required by the complex approach. These obstacles lie not only in AMR and biological vulnerability, but also in many other care deficits that have a major impact on prognosis [27].

  The next step is to turn obstacles into opportunities for improvement, and thus to generate and

promote, here and now, as soon as possible, specific initiatives that have been shown to have a positive impact on patient outcomes, specifically targeting each of the obstacles or problems identified. These initiatives must be based on the continuous improvement of existing resources and on better and wider access to innovation.

Finally, they must be translated into concrete, measurable and monitorable operational objectives (surveillance), which can be implemented (dissemination), and are capable of demonstrating their impact on clinical outcomes.

Lastly, and very importantly, it is worth highlighting the significance, within this improvement process, of the proper establishment of strategic alliances between all stakeholders involved in the healthcare system (academia, the pharmaceutical industry, government and healthcare professionals).

The available evidence indicates that processes of this type, such as the approach to HIV, tuberculosis, candidemia bundle or some ASPs, can be associated with tangible clinical benefits, which reinforces the viability and necessity of this strategic refocusing.

In summary, we believe that, in this context (at-risk patients with severe infections), it is necessary to take a step further and move from the conceptual framework to the operational level, where decisions are made in real time and their consequences are immediate. This document is therefore conceived as a proposal deliberately geared towards clinical practice, designed to address the complexity inherent in severe infections in these at-risk patients. This is not about adding new layers of regulation, but rather about precisely identifying the critical points where therapeutic effectiveness is gained or lost. From here, the focus shifts to early diagnosis (clinical and microbiological), risk stratification, and the selection of the treatment most likely to have a clinical impact. In the following sections, the reader will find a structured elaboration of these elements, with the aim of facilitating faster decisions, based on sound scientific grounds, and more closely aligned with the actual reduction of morbidity and mortality. This implies accepting that, in this scenario, effectiveness is not an option, but a clinical imperative.

3. ASP-COMPLEX: an ASP aimed at improving the effectiveness of infection treatment

With the aim of proposing initiatives capable of improving the prognosis of severe infections, we have followed a process based on intellectual and scientific reflection, the analysis of our experience, and consensus-building among panel experts, including the ASP-COMPLEX course and forum held at the SEIMC Satellite Campus in May-June 2025. This has led to the development of **15 proposals** targeted at three critical decision areas in the management of severe infections in at-risk patients (**Figure 2):**

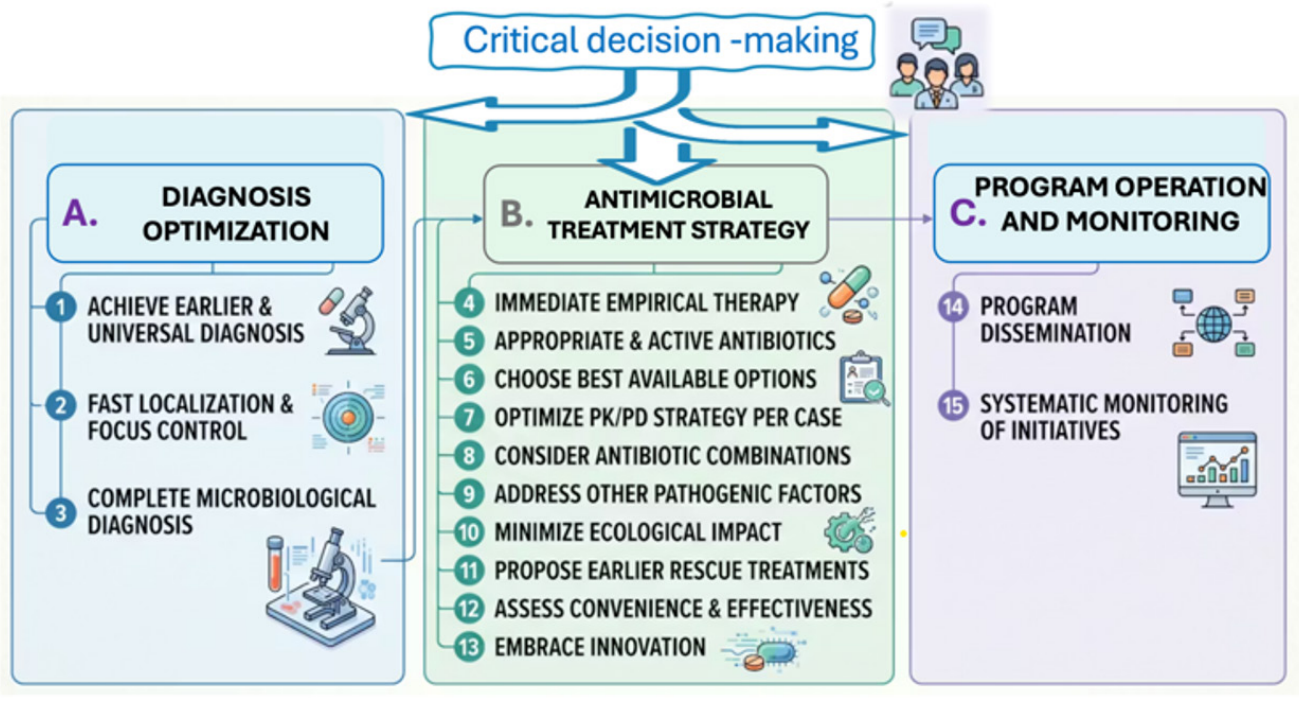

Figure 2. Overview of 15 proposals for managing better severe infections in high-risk patients

A) The initial phase: focused on the clinical diagnosis of severe infection and the establishment of a microbiological diagnosis.

B) The point of prescription: when antimicrobial treatment is prescribed and its degree of efficacy is determined.

C) Programme dissemination and surveillance: initiatives to make the programme operational and to monitor its impact on clinical outcomes.

A. Proposals to improve clinical and microbiological diagnosis of severe infection

In the clinical management of infections, the primary objectives are to assess severity, which stratifies the risk of morbidity and mortality and facilitates rapid access to empirical treatment; to identify the source of infection, which facilitates more targeted empirical treatment and better control of the infectious process; and to determine the microbiological aetiology, which allows for the appropriate antimicrobial treatment. In at-risk patients, delays or inaccuracies in recognising a serious infection, its microbiological aetiology, and the septic focus have a significant impact on prognosis. Therefore, these constitute critical points for optimisation:

A1. Achieving earlier and more widespread diagnosis of severe infection

Recent consensus documents in the field of emergency medicine have emphasised that, despite advances, the early recognition and optimisation of the initial management of severe infection remain significant areas for improvement in clinical practice [120]. The sensitivity of the best-validated current protocols and guidelines for diagnosing severe infection is poor, particularly in the most at-risk patients and those at high risk of harbouring AMR [120-126]. The combined use of clinical scales and biomarkers has proven useful in identifying severe infection, although with limitations in sensitivity and applicability in certain patient subgroups [127]. Our proposals to achieve an earlier and more universal diagnosis of severe infection are:

1. **Stratify severity using a multimodal approach based on the patient's degree of vulnerability, clinical features and biomarkers**:

    - Incorporate an appropriate assessment and categorisation of vulnerability into all diagnostic protocols for sepsis/severe infection [27, 100-101, 122-123, 127].

    - Lower the clinical diagnostic threshold in these at-risk patients. The presence of any vulnerability criterion in a patient with suspected infection and a SOFA score < 2 would necessitate continued monitoring and the search for other criteria for severe infection which, even at the cost of a loss of specificity, are more sensitive, such as SIRS, NEWS, NEWS-2, MEWS, critical elevations in biomarkers [128-131], predictors of bacteraemia [132], AI, etc.) [120-126, 132-134].

    - Incorporate new biomarkers of severe infection, such as PCT, MDW, MR-proADM; the latter two may be useful in elderly patients for the early detection of severe infections and risk stratification [134-136].

2. **Consider the incorporation of new technologies based on big data/machine learning/ artificial intelligence.** Moving beyond the traditional approach based on the development and application of clinical scales and biomarkers, and facilitating automation, accuracy and independence from training, the development of AI-based algorithms has shown potential for improving the early detection of severe infection and optimising clinical decision-making in real time [137-141].

A2. Identifying and controlling the source of infection more rapidly

Identifying the source of infection facilitates a more targeted empirical treatment using a syndromic approach, and sets a time limit for optimising control of the focus—apart from antibiotic therapy—when it requires additional measures (drainage or instrumental or surgical debridement, replacement or removal of catheters, tubes, prosthetic material, etc.), which, if delayed beyond the first 6 hours after diagnosis, has been shown to worsen the prognosis [142-145].

A3. Achieving an earlier, more comprehensive and accurate microbiological diagnosis

'Etiological uncertainty' increases the risk of providing inappropriate treatment; and, consequently, in vulnerable and critically ill patients, the risk of mortality [125-126]. To optimise microbiological diagnosis, we propose:

1. **Fully integrating Microbiology Departments** into clinical decision-making, acting as strategic partners and not merely as data providers. This requires that hospitals treating patients with sepsis consider continuous and comprehensive 24/7 care coverage as standard, something that is still far from reality (only 10% of European centres have a continuous microbiology service, although they have 80% adherence to other sepsis care processes) [146].

2. **Incorporating the PRODIM concept** (Programmes for the Optimisation of Microbiological Diagnosis) to maximise the clinical value of microbiological diagnosis [147]. It is not just a question of which test we use, but of for whom, when and why we use it. This represents the adaptation of microbiology to clinical needs and health outcomes, prioritising the actual impact on the patient and their prognosis over technical metrics.

3. In this multidisciplinary context, selecting **initiatives that can improve the effectiveness of infection treatment in the short term**, such as the following:

    - **Incorporate new microbiological techniques for rapid, accurate and comprehensive diagnosis**. Conventional techniques, which remain the gold standard for epidemiological diagnosis and surveillance, have significant limitations in at-risk patients (primarily the delay inherent in microbial growth, but also sensitivity that is highly dependent on the source and quality of the sample and on prior antibiotic therapy, etc.) [148-150]. The diagnostic yield of blood culture is 10–20%, and the development of rapid diagnostic techniques has accelerated and improved this to 60–70%, presenting a critical opportunity for optimisation [123]. Syndromic molecular platforms, such as those used in severe respiratory infections [151-153], central nervous system (CNS) infections [154-157], or severe sepsis [152, 158], allow the simultaneous detection of multiple pathogens and, in some cases, resistance genes, directly from clinical samples or positive blood cultures, with very short turnaround times [152, 158], with high analytical sensitivity, enabling the detection of slow-growing or difficult-to-culture pathogens, non-viable microorganisms following prior antibiotic therapy or due to nutritional or atmospheric requirements, intermittent or low-load bacteraemia, and co-infections that might go undetected with conventional techniques [151-152, 159].

      Furthermore, when integrated into well-structured and standardised diagnostic processes, they reduce interobserver variability and facilitate their implementation in settings where expert personnel are not always available. Rapid molecular genomic or proteomic techniques for identification (MALDI-TOF, syndromic panels with multiple gene targets) and phenotypic antibiotic susceptibility testing (AST) (using immunochromatography, GeneXpert, etc.) based on positive blood cultures [160–163], have demonstrated a reduction in time to appropriate treatment, lower exposure to broad-spectrum antibiotics, facilitation and justification of treatment escalation or de-escalation, and reduced mortality in some cases, particularly in vulnerable patients [160–161, 164–166]. Metagenomics and emerging techniques applied to clinical samples have shown promising results in selected settings, enabling the detection of unsuspected pathogens and emerging resistances; however, their availability is limited, their interpretation is complex, and their clinical impact is still under evaluation, so they should currently be reserved for selected critically ill patients [167–169].

      However, these advantages are accompanied by significant limitations, both in terms of sensitivity (for example, bacteraemia and fungaemia platforms such as Biofire® BCDI2 Panel from bioMérieux® rely on a prior positive blood culture result, which limits their impact to approximately 40–50% of sepsis episodes [149]); and in the interpretation of resistance mechanisms, as the absence of detection does not rule out relevant mechanisms not included in the panel, such as AmpC-mediated carbapenem resistance and impermeability in *Pseudomonas aeruginosa* [170]), as well as specificity (in non-sterile samples, such as respiratory samples, they may over-detect colonisation, particularly in patients on prolonged mechanical ventilation [159]; or also in the interpretation of resistance genes, the detection of a gene does not guarantee its phenotypic expression [170]), of spectrum, as there is heterogeneity in the targets available in each panel, and results must be assessed bearing in mind that there will always be potential targets not included in the panel we use), or in relation to efficiency (their high costs and the complexity of their interpretation necessitate continuous monitoring of the quality of their use – the key is not to have more tests, but to know for whom, when and how to apply them, which requires constant training and communication – and this must always be carried out within diagnostic stewardship programmes [147, 158, 171-175], and, for now, focused on at-risk patients for whom early information may influence clinical management and outcomes).

    - **Optimise the local microbiological profile** (the cumulative susceptibility). Traditional mapping has significant limitations, and in order to turn it into a useful tool for improving empirical

aetiological coverage to >90–95%, more and better assessment and information would need to be incorporated on aspects such as the following: stratification by hospital areas/departments, source of infection, patient type and vulnerability, and clinical syndromes; on the relative frequency of microorganisms in each syndrome, polymicrobial infections, epidemic outbreaks (in real time), interpretation of the MIC focused on its impact on clinical outcomes, resistance mechanisms, the relationship between weighted incidence and susceptibility; and, very importantly, on new antibiotics and combination regimens. New techniques combining clinical and microbiological data (Weighted-Incidence Syndromic Combination Antibiogram -WISCA) would help us predict the likelihood of coverage by a specific antibiotic therapy (using one or more antibiotics) for a specific infection [176]. Such an optimised map would be very useful for substantiating and configuring local antimicrobial treatment guidelines in real time.

- **Place greater focus on the post-identification phase of microbiological diagnosis**, with the aim of better determining, on an individual basis and in real time, the most effective antibiotic treatment for isolated bacteria exhibiting the most severe resistance phenotypes.
- There are new microbiological aspects which, although still in the future, could be considered within the context of this ASP-COMPLEX, such as monitoring changes in bacterial load and controlling the inoculum, the emergence of AMR during treatment, etc.

B. Proposals for more effective prescribing of antimicrobial therapy

The primary objective of this document is to promote therapeutic effectiveness—that is, prescribing treatments with the highest degree of anticipated effectiveness available for at-risk patients with severe infections. This is because the absence, delay, confusion, or complacency in the intention to design effective treatments is very common and has a significant impact on prognosis. In operational terms, therefore, the goal is to achieve a commitment to effectiveness at all levels that influence and contextualize decision-making regarding antimicrobial treatment: from the prescriber's perspective to health administration, including expert institutional support (ASPs, guidelines, surveillance, etc) and training and research [177]. To this end, we propose measures that have demonstrated their ability to improve clinical outcomes, as shown in **Table 1**.

B4. Immediate initiation of empirical antibiotic therapy

Delays in starting treatment following the diagnosis of a severe infection are critically important, as they significantly and rapidly worsen the prognosis, and, furthermore, are very common [121, 123, 178-186]. For this reason, the immediate initiation of antibiotic therapy in these patients must be an absolute priority, which must be implemented and maintained at all times.

Although the point from which the time to the start of antibiotic treatment should be measured is the onset of the infection and its symptoms, in practice this must be shifted to the time at which the patient first contacts the health services.

Even though this introduces an obvious bias, the accumulated evidence shows that in severe infections, the speed of treatment initiation, as a continuous variable, leads to significant benefits in terms of survival [121, 123, 178, 180-185]. Thus, in the case of bacterial infections, current evidence suggests that initial or empirical antibiotic therapy should be started: within 1 hour if there is septic shock or definite or probable sepsis; or within 3 hours if sepsis is possible and cannot be ruled out within that time [121, 123, 178, 180, 184].

In special populations, such as oncohaematological patients with febrile neutropenia, a time threshold of as little as 30 minutes has even been established for the initiation of effective antibiotic treatment [187]. In addition to prescribing empirical antibiotic therapy early, it is advisable to monitor and confirm its correct administration, both timely and appropriate, by nursing staff. The same applies to acute and severe viral infections, albeit with different timing. For example, in influenza (and recently in SARS-CoV-2 infection), although it is well established that initiating antiviral treatment in at-risk patients within the first 48 hours of symptom onset reduces morbidity and mortality, this is a very uncommon practice [186].

B5. Selection of an appropriate, active and effective empirical antibiotic therapy

The rate of inappropriate treatment, defined as prescription of a treatment that is inactive or ineffective against the causative agent, in the management of severe infections is very high (15–50%), particularly if the infection is caused by MDR bacteria (>40%) [80, 84-85, 183, 188-205]; and this occurs in the most difficult-to-treat infections, even when guidelines are followed in 90% of cases (87% [84] – 92% [85]). Furthermore, this is a problem that is not improving over time [85, 183, 188, 197, 199, 201, 203-205].

In these infections, ineffective empirical treatment is associated with a significant increase in mortality [80, 84-85, 183, 188-197, 199-205]. Thus, it is imperative to improve the coverage of empirical treatment that we advocate in routine clinical practice, which should be above 90–95% in this patient group. This can only be achieved by providing, in guidelines and expert recommendations, treatments with a better PK/PD profile (i.e. better antibiotics, strategies and combinations), guidance on empirical treatment based on recent surveillance cultures of rectal, oropharyngeal or mucocutaneous swabs, previous colonisations or infection; and AI-based predictive tools such as clinical decision-making and antibiotic selection support systems, which have been shown to achieve greater therapeutic efficacy, a reduction in complications and significant decreases in mortality [85, 188, 200-206].

From efficacy to effectiveness

In patients with severe infection and high vulnerability, the quality of empirical prescribing should not be judged solely on its probability of microbiological coverage, but rather on its ability to elicit an early, robust and effective therapeutic response in a biologically fragile host.

In this context, the effectiveness of antibiotic therapy encompasses at least the following dimensions [207-214]: 1) spectrum or coverage of the likely pathogen; 2) intrinsic bactericidal capacity, derived from its PK/PD profile; 3) optimal timing and speed of initiation; 4) sufficient PK/PD exposure at the site of infection; 5) bactericidal activity in scenarios involving high inoculum, resistance, tolerance, persistence or high virulence, or an altered immune context in the host; 6) complementarity in the use of combinations – which determines the additive and synergistic effects of the combinations; and 7) feasibility of maintaining an effective, safe and sustainable therapeutic strategy during the first 48–72 hours. This perspective allows us to move beyond a binary interpretation of antibiotic therapy as 'active' or 'inactive' and shifts clinical reasoning towards a scale of probability of therapeutic success and effectiveness (**Figure 3**).

And furthermore, it would serve to explain, at least in part and aside from critical vulnerability, the mortality that occurs in patients receiving theoretically

Table 1. Factors influencing therapeutic efficacy in infections

Domain	Variable	Expected clinical impact	Practical implication
Host	Immunosuppression, frailty, ARC, RRT/ECMO	Increased risk of severity Extreme variability in drug exposure Risk of underdosing or toxicity	Enhanced severity detection Accelerated and intensified therapeutic response Use of TDM, adjustments for dynamic renal and hepatic function, and loading doses
Pathogen	AMR, High inoculum, Persistence, Biofilm, Virulence	Elevated MIC Therapeutic failure due to lack of bacterial eradication	Selection of more effective therapies Optimization of PK/PD indices (*f*AUC/MIC) Therapies targeted at biofilm, persistence, and virulence
Source	Lung, CNS, Endocardium, Abdomen, Urinary tract, Prosthetic material	Varying degrees of drug penetration depending on tissues Formation of infectious sanctuaries	Drug selection based on tissue diffusion High doses to overcome barriers (e.g., blood-brain barrier) and source control (surgery)
Treatment	Onset, coverage, PK/PD, combination therapy, toxicity	Delayed onset increases mortality Sub-exposure promotes the emergence of resistance	Early initiation of empirical therapy with maximum coverage (>90-95%) and efficacy PK/PD optimization Response assessment at 48 h (for adjustment, de-escalation, or rescue, and duration planning)
System	Drug access, rapid and precise microbiology, ASP, nursing	Logistic or diagnostic delays invalidate the best pharmacological strategy	Implementation of rapid microbiological diagnostics (MALDI-TOF, PCR...) Standardised administration protocols and support from ASP teams

ARC: Augmented Renal Clearance; RRT: Renal Replacement Therapy; ECMO: Extracorporeal Membrane Oxygenation; TDM: Therapeutic Drug Monitoring; MIC: Minimum Inhibitory Concentration; AMR: Antimicrobial Resistance.

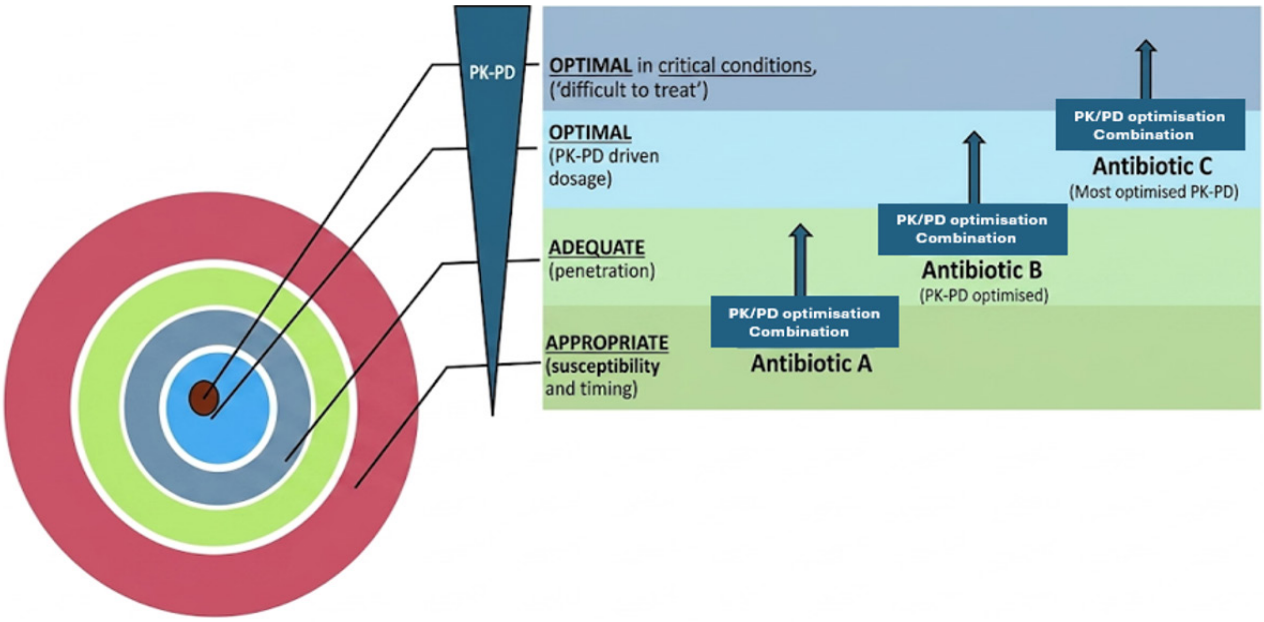

Figure 3. **From efficiency to effectiveness, from appropriate to optimal. Adapted from Ramasco et al. [177]**

appropriate antibiotic therapy (active against the causative microbial agent) [215]. This is a form of mortality that is likely to be common, yet relatively unnoticed and insidious, stemming from the difficulty in recognising and acknowledging the existence of this gap between efficacy and effectiveness. There is a substantial body of literature, including high-quality evidence [216-219], that illustrates this problem.

Thus, the aim is to understand that each antibiotic exhibits these characteristics to varying degrees, generating different levels of efficacy that are distributed across a hierarchical, stratified scale. Consequently, among the antibiotics active against the causative agent, some are better or more beneficial than others for curing a specific infection in a specific patient and at a specific stage of the infection, such as hyperinflammatory vs immunoparalysis; microbiologically quiescent vs active rapid-growing, haematogenous vs compartmentalised, etc. [216-219].

Therefore, in this scenario, given the need to move from efficacy towards effectiveness and to ask ourselves how to achieve an effective treatment or the most active one possible from among those available for this type of patient, our proposals to improve effectiveness are as follows:

B6. Selecting the best possible options from among the available antimicrobials

In general, the best possible options for achieving effectiveness in the most difficult and demanding cases are the new antibiotics, as they are the result of innovation and a design focused on continuous improvement. Consequently, compared to their predecessors, they tend to have more favourable PK/PD profiles, which, by enhancing their bactericidal and microbial eradication capabilities whilst minimising their ecological impact and toxicity, confer clinical advantages that have been demonstrated in certain difficult or complex scenarios (**Figure 4**) [213, 216-217, 220-357].

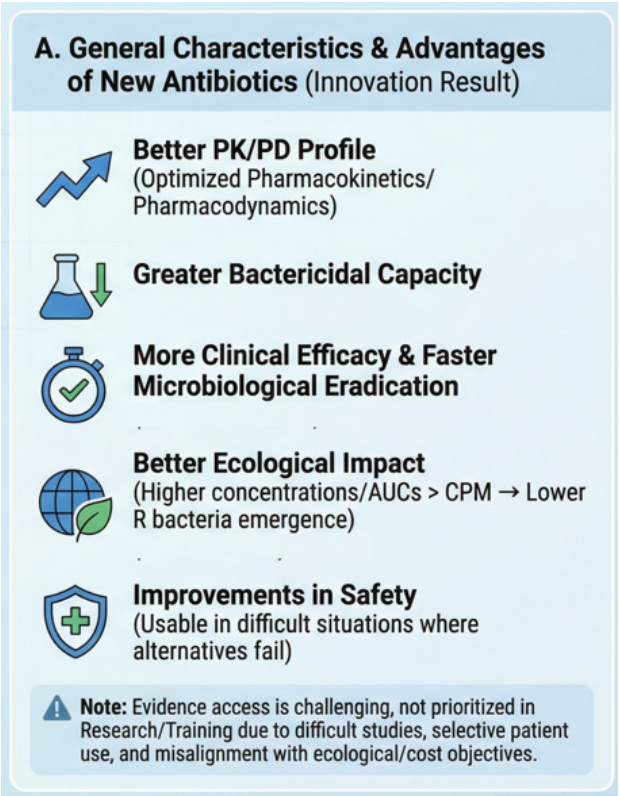

Figure 4. **Theoretical advantages of new vs. classic antibiotics**

Table 2. Comparative overview of new vs. classic antibiotics

Hierarchical scale of effectiveness	Microorganism / Scenario
Cloxacillin > Vancomycin	MSSA [220–223]
Daptomycin > Vancomycin	MRSA/MSSA [224–228]
Oritavancin (and dalbavancin) **>** Daptomycin **>** Delafloxacin > Cefazolin/Cloxacillin **>** Vancomycin **>** Tigecycline and Linezolid	*S. aureus* [220, 229–234] *
Ceftaroline > Ceftriaxone	*S. pneumoniae* [235–240]
Fluoroquinolones > third- and fourth-generation cephalosporins > piperacillin/tazobactam	In the absence of resistance to fluoroquinolones, Enterobacterales and *P. aeruginosa* [213, 241–244] *
Carbapenems > 3rd/4th generation cephalosporins > Piperacillin/tazobactam	Enterobacterales [216–217, 245–254] (Not applicable if urinary tract infection caused by Enterobacteria with ESBL)
Ceftolozane-Tazobactam > Meropenem **>** Ceftazidime-Avibactam **>** Ciprofloxacin **>** Ceftazidime/Cefepime **>** Piperacillin-Tazobactam	*P. aeruginosa* [255-261] *
Carbapenems > Fluoroquinolones **>** 3rd/4th generation cephalosporins **>** Piperacillin-Tazobactam	In terms of efficacy against infections with a high microbial load (inoculum effect) [241, 251,262–263] *
New antibiotics (*Dalbavancin/Oritavancin* [264–271], *Ceftaroline* [235–240, 272–277], *Ceftobiprole* [278–280], *Ceftolozane-Tazobactam* [281–285], *Ceftazidime-Avibactam* [286–292], *Meropenem-Vaborbactam* [292–298], *Cefiderocol* [292, 299–313], *Imipenem-Relebactam* [314–316], *Delafloxacin* [317–322], *Cefepime-Enmetazobactam* [292, 323–325], *Plazomicin* [292,326], *Eravacicline* [327–331], *Aztreonam-Avibactam* [332–336], *Rezafungin* [337–338], etc.) [292, 298, 339–355] **> conventional or pre-existing antibiotics**	In general, for severe infections at high-risk patients
Carbapenems > Comparators (Piperacillin-Tazobactam, 3rd/4th-generation cephalosporins)	With proven clinical impact [217, 253, 356–357] *

Hierarchical positioning was based on available clinical evidence together with in vitro bactericidal activity assessed by time-kill curves and PK/PD data. And iti is always relative and contextual (see text).

*Indicates that AI has been used in the analysis of that algorithm.

Although the scientific evidence demonstrating their potential benefits is extensive and robust, access to this evidence is generally not straightforward. They are not prioritised either in research—because they require studies that are difficult to conduct—or in training—because they are applicable only to a select group of patients and are at odds with the predominant ecological and cost-containment objectives. However, the lack of top-quality evidence should not prevent access to a wealth of other scientific knowledge that helps us not only to guide but also to better prioritise the varying degrees of effectiveness of antibiotics across the multiple clinical scenarios encountered in clinical practice.

Under comparable conditions and in specific scenarios, some of these studies suggest that certain groups of antibiotics are relatively more effective than others. Examples of a sufficiently well-established hierarchy, albeit with varying degrees of strength, are shown in **Table 2**.

The ranking of antimicrobials should always be interpreted in context and not as indicating universal superiority. The relative effectiveness of an antibiotic can vary substantially depending on the infectious syndrome, control of the source of infection, the size of the bacterial inoculum, the degree of specific bacterial resistance present and, most importantly, penetration into the target compartment. Therefore, any proposal for therapeutic prioritisation should explicitly incorporate the site of infection and the anticipated exposure at that site. In other words, in complex infections, it is not enough to choose a microbiologically active

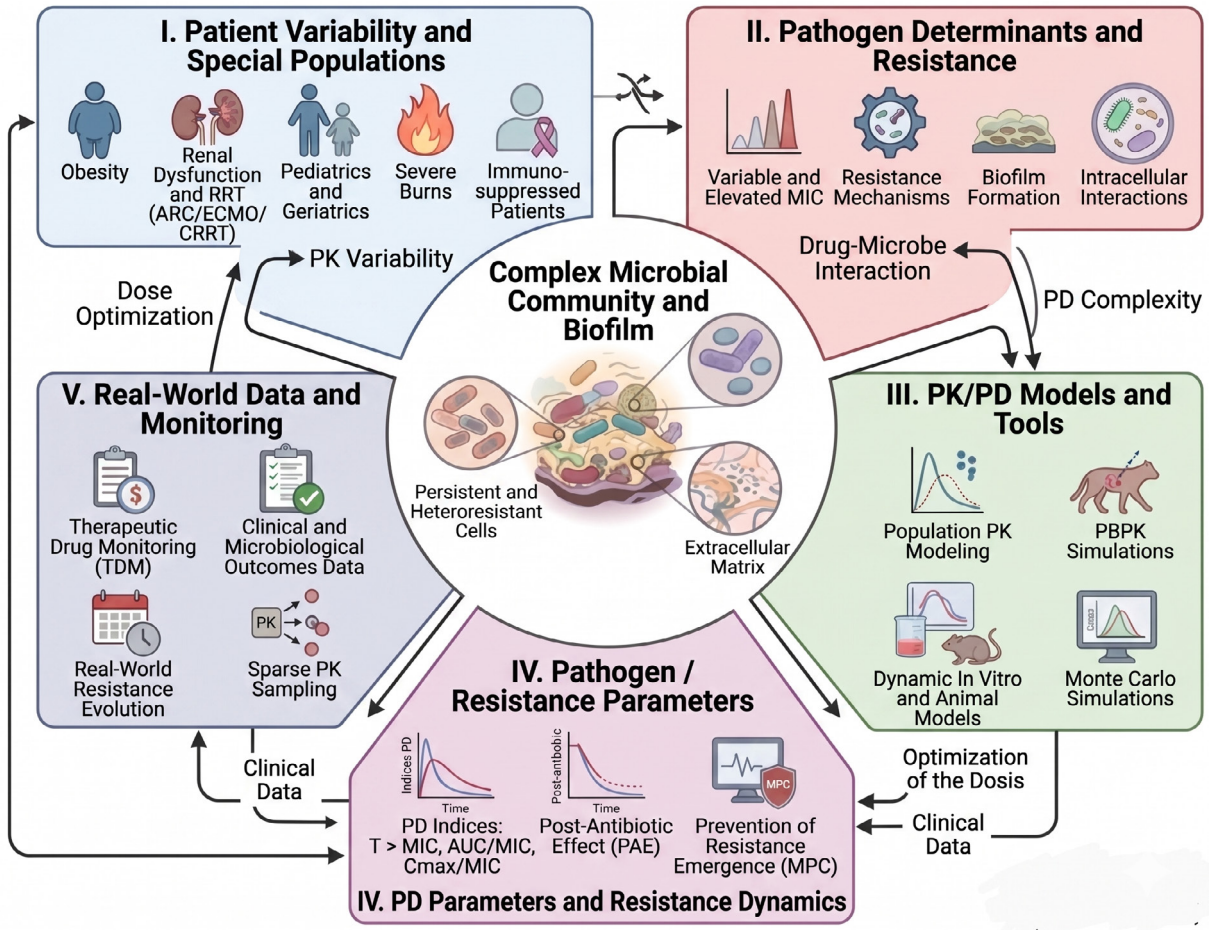

Figure 5. **The complexity of optimising antibiotic therapy for severe infections**

antibiotic: it is essential to select the one that offers the best effective exposure at the site where the infection is occurring. [358-360].

It is therefore reasonable, in the case of severe and difficult-to-treat infections in the most at-risk patients, to consider that new antimicrobials may improve the effectiveness of treatment and that their selection may improve the prognosis of these infections (**Figure 3**).

B7. Design the best possible strategy tailored to each individual case, based on optimising the PK/PD profile

The aim is to tailor treatment by individualising antibiotic dosages and regimens to meet the complex and demanding conditions of these patients, their specific infections, and the underlying pathogens.

Increasing doses, either per dose or by increasing the number of doses, depending on whether the antibiotic is dose- or time-dependent, prolonged or continuous infusions, initial loading doses, and pharmacological and microbiological monitoring of their effects are well-established optimisation strategies for a wide range of antibiotics in many infection models [361-369] (**Figure 3**).

PK/PD optimisation takes on even greater relevance in subgroups with particularly complex pharmacokinetics, such as critically ill patients with renal hyperfiltration, continuous renal replacement therapy, ECMO, obesity, severe hypoalbuminaemia, extensive burns, or massive expansion of the extracellular space. In these scenarios, standard dosing regimens are particularly vulnerable to under-exposure and, consequently, to treatment failure. Thus, ASPs focused on effectiveness must incorporate specific pathways for advanced pharmacotherapeutic validation, therapeutic monitoring where available, early review of doses (loading and subsequent) and infusion (standard, extended or continuous), and a structural role for the clinical pharmacist in the daily audit of highly complex treatments [370-372] (**Figure 5**).

PK/PD optimisation is a pharmacological issue and can therefore benefit significantly from the contribution of the pharmacy department. The ability to audit prescriptions from a PK/PD perspective, to provide real-time guidance on achieving pre-established and validated PK/PD targets, to monitor antimicrobial concentrations), to help minimise drug interactions and toxicities, and to make the necessary pharmacological adjustments in patients with

comorbidities that alter antibiotic metabolism, and to rescue beta-lactam agents through a beta-lactam allergies delabelling programme offers significant opportunities for optimisation, just as the correlation of PK/PD parameters with the quantitative evolution of the bacterial load may also improve effectiveness. We must therefore recognise that pharmacy is a key strategic partner in the pursuit of effectiveness.

B8. Consider the improvements in the PK/PD profile that combinations of antimicrobials can offer

Historically, combinations of antimicrobials have proven more effective than monotherapy in treating a range of 'difficult-to-treat' infections, includin HIV infection, hepatitis C, tuberculosis, brucellosis, Q fever, endocarditis, malaria, toxoplasmosis, etc. They have also proven effective in the most severe infections caused by multi-resistant Gram-negative bacteria [80, 85, 200, 202, 257, 345, 369, 373-394], multi-resistant Gram-positive bacteria [395-408] and fungi [409-412].

Combination therapy is a strategy of selective intensification in situations with a high risk of early treatment failure, such as septic shock, suspected MDR pathogens with high attributable mortality, persistent bacteraemia, incomplete or delayed control of the source of infection, infection with a high bacterial load, certain forms of profound immunosuppression, the presence of toxins and other virulence factors, etc. Within this framework, combination therapy can lead to improvements in efficacy (**Figure 3**) that may be critical in the initial treatment of the most complex or difficult-to-treat infections, even in the case of new antibiotics [313, 385-394]. This involves not only broader coverage, but also a faster reduction in the bacterial load, enhanced PK/PD, inhibition of toxin and superantigen synthesis, and prevention of resistant mutant subpopulations [188, 288, 413-420].

The drug interactions involved in combination therapy and their relationship with the mechanisms of microbial resistance are highly complex, have not been sufficiently explored, and give rise to uncertainties that call for caution [421-425]. Furthermore, they can lead to drug antagonism and increase the potential for toxicity and other undesirable drug interactions. However, there is a wealth of literature showing that combinations can hinder the emergence of resistant bacteria during antibiotic treatment [81, 354-355, 420, 425-429]: 'Perhaps the most important use of combination chemotherapy is in attempts to suppress the emergence of resistance' [354-355].

However, although we are operating in a context of unacceptably high mortality [80, 215] and assume that combination antibiotic therapy can offer clinical and ecological benefits, its uptake in clinical practice has been slow and insufficient, perhaps unduly hampered by the inertia generated by the paradigm linking antibiotic pressure to the development of AMR [80].

Its adoption could be facilitated by the assumption that every indication for combined antibiotic therapy should be subject to early re-evaluation and an explicit simplification strategy once microbiological and clinical uncertainty has diminished. Furthermore, it is necessary to encourage and maintain close scientific monitoring of the risks and benefits of this strategy.

B9. Consider other pathogenic factors that influence the effectiveness of antimicrobial treatment

Other pathogenic factors, both microbial and host-related, in addition to AMR, can increase the risk of treatment failure, such as virulence, persistence, including in biofilms or 'biological sanctuaries', or immune dysfunction generated by the microbial agent and/or the host's immunoregulatory genotype/phenotype, which may manifest as hyperinflammation, immunoparalysis, etc.

This is a real problem and, although it is an underexplored or insufficiently explored area [430-432], its influence on therapeutic effectiveness would compel us to give it greater consideration and to delve deeper into the selection of patients who might benefit from treatments better adapted to these types of factors.

On the one hand, we must pay greater attention to potential anti-inflammatory and immunomodulatory adjuvant therapies, which combat hyperinflammation or immunoparalysis, or interfere with pathogenic processes, such as bismuth, gamma interferon, checkpoint inhibitors such as anti-PD1, etc. On the other hand, we must deepen our understanding of, and put into practice, how various antimicrobials address these virulence factors, such as the release of polysaccharides and other endotoxins; or better penetrate biofilms or sanctuaries and maintain their activity against persistent bacteria, or how they better adapt to the patient's inflammatory or immunological profile [430-432].

B10. Minimise the ecological impact as much as possible in every prescription

The emergence of AMR during exposure to antibiotics is their main adverse effect; it is cumulative in nature (it progresses easily and is very difficult to reverse), impacts prognosis in direct proportion to its presence, and is also very difficult to control. It is a highly complex and poorly understood issue, and we

have few tools to study it, few targeted studies, little regulatory scrutiny in this regard, and insufficient institutional surveillance. Multiple variables interact in the generation and development of AMR even when their use is appropriate: microbial factors (both individual and ecological), host factors (immune system, microbiome, genotype, habits, comorbidities, etc), and antimicrobial therapy factors (drugs, PK/PD strategies, duration) [59, 343, 354-355, 425, 428-429, 433-447]. It is important to note that the use of antibiotics merely selects for, rather than generates, resistance genes or clones that must already be present, within an altered ecological context that allows for clonal amplification, and under prolonged selective pressure. Moreover, any oversimplification of the problem (for example, 'more antibiotics = more resistance' or 'broad-spectrum antibiotics generate more resistance') is inaccurate and prevents valid predictions.

Although the ecological impact does not determine initial clinical effectiveness, as it does affect future effectiveness but not current effectiveness, and managing it is complex and difficult, its significance is such that every prescription of antibiotics must include an assessment of its ecological impact and of the ability to prevent the emergence of resistance during treatment [354-355]. Such an assessment should also be given greater weight in scientific research, in the marketing of antibiotics and within the health administration, through ecological impact monitoring systems [354-355].

Therefore, in a scenario such as that outlined in this document, which focuses on the pursuit of effectiveness through the intensification of antibiotic pressure, it is necessary to address the challenge of whether maximising therapeutic efficacy could fuel or drive AMR.

Minimising the ecological impact is a more demanding objective than achieving a cure. Clinical cure is achieved with a certain level of antibiotic pressure (exceeding PK/PD targets centred on the MIC, which, as it is prolonged, selects for and allows the development of more resistant subpopulations (which would require greater antibiotic pressure, with PK/PD targets centred on the Mutation Preventive Concentration (MPC) for their eradication).

However, these two objectives need not be mutually exclusive. The strategy known as 'front-loading', which proposes the initial use of the most active and eradicative treatments (with better PK-PD outcomes, which are generally provided by last-line antibiotics, combinations and new strategies – including therapeutic alternatives with adjuvants, inhibitors, potentiators, new formulations, immunomodulators, phages, gene therapies, biomolecules, new products proposed by AI…), administered over very short periods (for this purpose, ideally less than 5 days, probably sufficient up to 7 days), could be a good strategy for reducing the ecological impact, as it would reduce the initial microbial inoculum more rapidly and shorten the duration of selective pressure, whilst also enabling the elimination of more bacterial subpopulations with a higher AMR burden.

Although this strategy lacks sufficient clinical evidence, it is conceptually appealing and biologically plausible, and is supported by considerable experimental evidence [428-429, 441-442, 444-445, 448-455] (**Figure 6**), which, as long as it does not contradict existing clinical evidence, could help us to make this concept more operational and incorporate it into our recommendations.

We therefore propose that the restrictive nature of ecological control over prescribing practices should be adjusted, allowing for increased antibiotic pressure during the initial phase of treatment in this patient group. This would reduce the likelihood of prescribing suboptimal treatments which, paradoxically, could lead to greater pressure for the selection and spread of AMR and other ecological costs, since treatment failures lead to greater exposure to antibiotics and a greater progressive deterioration of the microbiota.

And since the selective pressure of antibiotic therapy, regardless of its complexity and difficult predictability, increases with the duration of exposure, we have better opportunities for ecological control than those affecting the choice of empirical treatment, such as the reductions in exposure provided by early adjustment or de-escalation, and the reduction in treatment duration [194, 445, 447, 456-475]. This type of high-intensity, short-course antibiotic regimen—which, as we have already noted, may have a favourable ecological impact—should be subject to a formal review after 24 hours and a second, decisive review after 48–72 hours, taking into account haemodynamic trends, control of the infection focus, microbiological results, biomarkers, toxicity and PK/PD plausibility. This would serve to adjust or de-escalate treatment, and also to detect treatment failure early and activate rescue strategies without delay (which are all the more effective and ecological the earlier they are implemented). Thus, adjustment or de-escalation and rescue represent two complementary expressions of the same principle: rapidly adjusting antimicrobial pressure to the evolving biological reality of the case. Complementarily, the judicious and individualised adjustment of the duration of antibiotic treatment for each patient

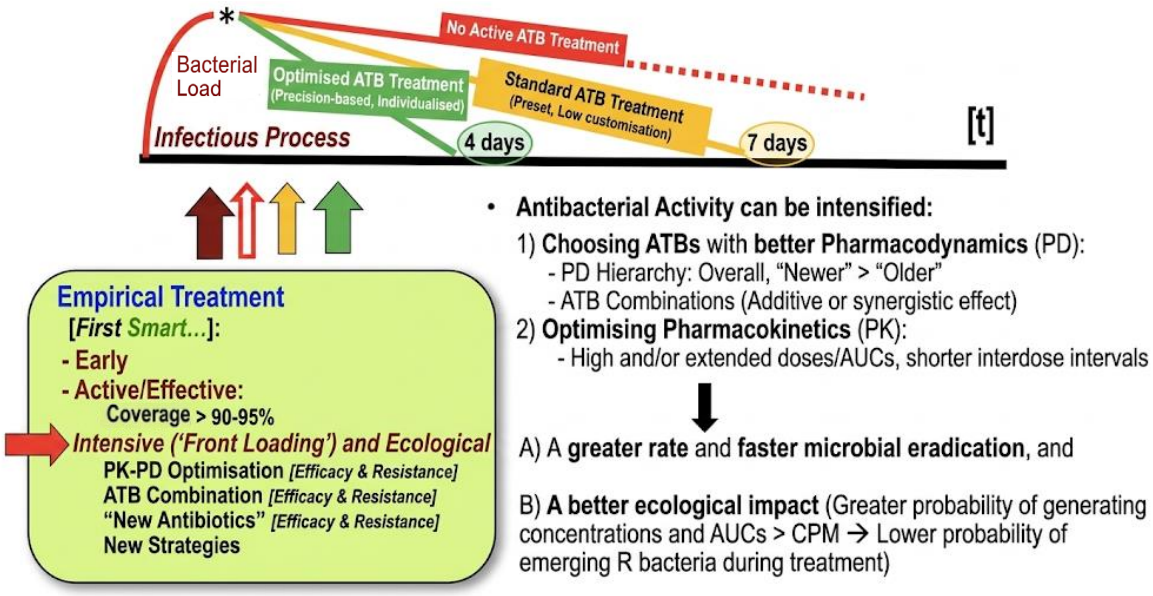

Figure 6. First smart: the "front loading" strategy can improve effectiveness and ecological impact. Partial data obtained from Paterson IK et al. [445]

and episode is another decisive factor in reducing its ecological impact [194, 445, 447, 456-475].

B11. Consider rescue therapy at an earlier stage

It is important to monitor the efficacy of antibiotic treatment in this type of infection and patient and to define treatment failure (and the need for rescue therapy) within the first 48–72 hours of treatment [476]. In this patient group, the best definition of treatment failure is the absence of significant signs of improvement within the first 48–72 hours of treatment [194, 445, 449, 465-467, 476-479].

In patients who fail initial treatment and have multi-resistant Gram-negative bacteria (GNB), a delay (> 4–5 days) in prescribing rescue therapy with the best available antibiotic options is associated with significantly lower survival, 3–5 times lower [216, 285, 290, 302, 305, 308-312, 317].

It is therefore important to rapidly incorporate the best antibiotics and therapeutic strategies into the guidelines and protocols for empirical rescue treatment for at-risk patients with severe infections.

B12. Assessing the importance of convenience in effectiveness

Investing in therapeutic convenience can improve the quality of our interventions and their outcomes. Therapeutic convenience should not be regarded as a secondary or merely logistical attribute, but as a clinical determinant of effectiveness, particularly during phases of care transition. The availability of simplified administration formulations, agents with a prolonged half-life or oral alternatives with high bioavailability can reduce delays, administration errors, loss of adherence, avoidable hospital stays and complications related to vascular access. In selected patients, these strategies allow for the maintenance of adequate therapeutic intensity beyond the initial critical period and facilitate models of shortened hospitalisation, outpatient continuity, and outpatient parenteral antimicrobial therapy (OPAT) with greater safety and less organisational friction [266-267, 480-484].

These new formulations reflect scientific and technical progress in pharmacological optimisation (representing the pinnacle of PK-PD optimisation); therefore, in addition to advantages in terms of safety, convenience, adherence, cost-effectiveness and quality of life, they have demonstrated benefits in clinical effectiveness [266-267, 485-489].

B13. Give greater and more effective consideration to the benefits of innovation

In the face of the major problem posed by the rise in AMR and the trend in infection-related mortality, the WHO's programme priorities—based on awareness-raising, surveillance, prevention and optimisation (of existing resources)—are not delivering the expected results [23-29]. There is a need to complement them with a more decisive push towards the incorporation of innovation that is adaptable, sustainable, anticipatory, parameterised, scalable and operational or usable, the benefits of which can be rapidly transferred to patients [490-494] (**Figure 7**).

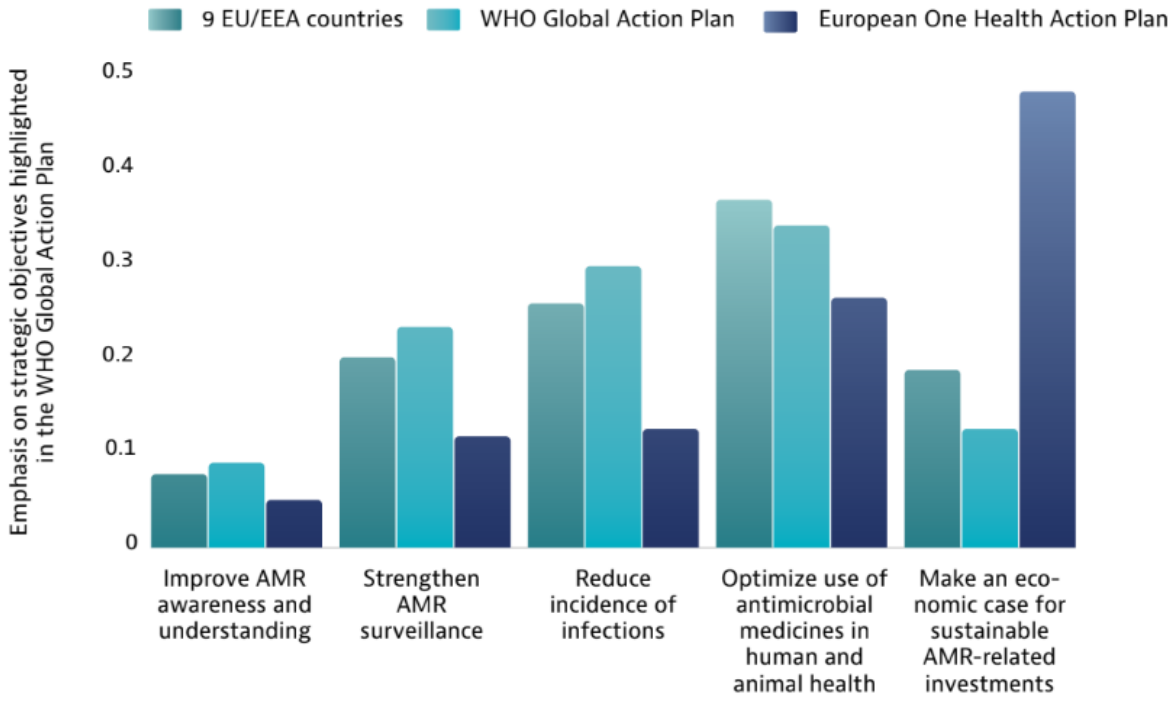

Figure 7. **The critical importance of innovation. Obtained from OCDE, 2022 [492]**

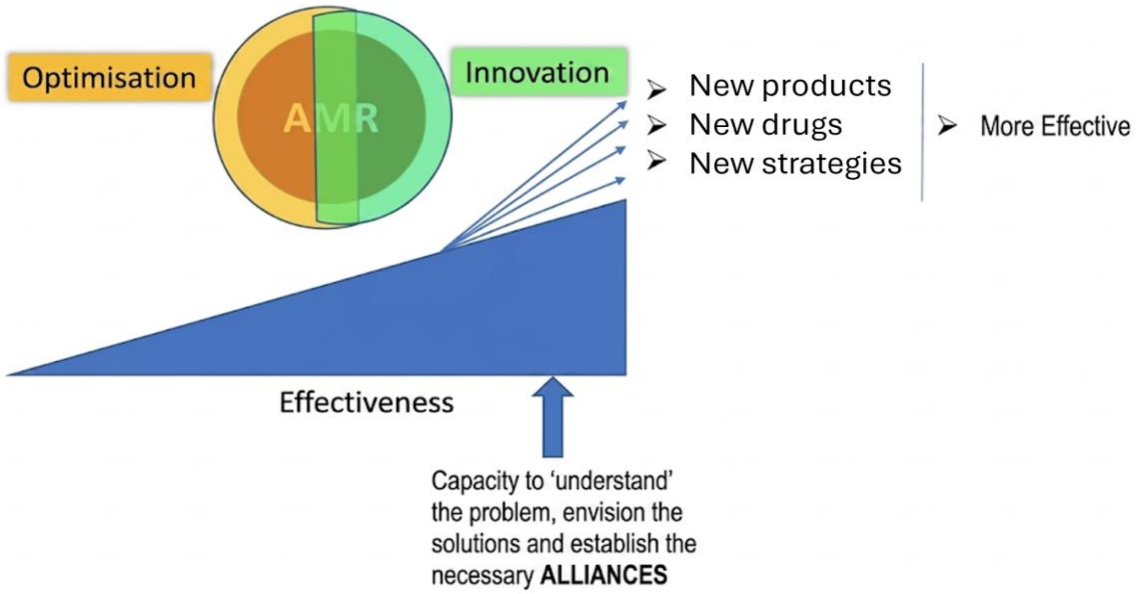

Figure 8. **Innovation and effectiveness**

However, accessing innovation is a highly complex and demanding process, with numerous critical points that must be managed effectively to ensure success (**Figure 8**).

1) **In the generation of innovation**:

   a. **Political awareness of the need for innovation**, on which research and development, budgets depend.

   b. **Management and direction of scientific research**, which, in the field of infections, has not evolved in line with needs. There has likely been a lack of cooperation between the various collaborating stakeholders (academics, government, healthcare professionals, pharmaceutical industry), and the ability to establish appropriate partnerships would be a significant advantage in addressing this

issue. In our field, it is often considered that 'partnering' with the pharmaceutical industry may undermine the quality of research due to the bias caused by its commercial interests. However, in the real world, it has become evident that economic interests, within a competitive environment and an appropriate regulatory framework, drive progress more—and probably better—than disinterested public initiatives operating 'outside the competition'. Is it better to use public funds for independent research into new applications for older, commercially 'orphaned' antibiotics [495], or to collaborate with the pharmaceutical industry on research aimed at optimising the use of new antibiotics, thereby prolonging their effectiveness and clinical utility [444, 446, 452, 496]? And which of these two types of research will benefit the patients on whom this document focuses sooner and more effectively?

A methodological review of research processes is also required, which could, for example, broaden, deepen and accelerate the research we need to improve the effectiveness of antimicrobial treatments, as is being done with the integration of AI into such methodology (for example, by investigating, through 'de-extinction', antibacterial molecules derived from the microbiomes of extinct animals, or by mining microbial DNA, etc., which is yielding promising and transferable results in far less time than in traditional research) [67, 497-502].

c. **Funding:** Research is very costly. The prevalence of restrictive policies jeopardises the necessary financial return required [58-59], hinders new investment, and deters and drives away research staff [503], whilst also stifling the necessary diversification and forward-looking nature of research. At present, it seems necessary to review the financial model underpinning the acquisition of innovation, which should probably be refocused more towards 'payment based on the product's value to the healthcare system' or 'outcome-based' rather than solely on sales volume [504-508]. As in the previous point, effective coordination between the various stakeholders involved would provide competitive advantages. A well-understood, managed and governed public-private partnership, as well as one that is transparent and meritocratic, continues to appear a reasonable opportunity to improve access to innovation.

d. **Translating research into operational innovation:** The process of moving from research to the provision of healthcare products capable of addressing unmet needs in a timely and appropriate manner is highly complex and beyond the scope of this document, yet it is fundamental. In the following section, we discuss how this issue affects professionals and what role they could play in accessing innovation in the best possible way.

2) **In the transfer of innovation to patients:**

a. **Scientific regulation**: The methodology required to generate scientific evidence is highly complex, to the extent that it jeopardises access to the innovation we need. To make scientific information more actionable, there is a need for more efficient management of the scientific literature and a streamlining of regulatory requirements [509].

b. **Administrative regulation:** The advantage of restricting the use of innovative products to those backed by 'high-grade' scientific evidence is that, as well as promoting the appropriate use of these products, it reduces costs. Hence the enduring appeal of restrictive policies for administration, which constitutes another barrier to innovation that needs to be reviewed.

c. **Advocacy (by healthcare professionals and patients):** Although the prospect of transforming these processes and procedures from the perspective of frontline healthcare professionals seems, given their complexity and scale, highly challenging, the fact remains that these professionals have access—sometimes significant access—to each and every one of the agents and stages involved in generating and regulating innovation, and play a fundamental role in advocating for and transferring this innovation to patients. And these possibilities offer critical opportunities, and therefore clear responsibilities. Opportunities in the design of research and in the interpretation and translation of its results into real-world practice. Also, in advocating for and demanding a commitment from the authorities to jointly review the regulatory process and the financial model underpinning the adoption of innovation. And, finally, within the professional context itself, in healthcare institutions, to streamline and ensure that the transfer of the benefits of innovation to patients takes place in a timely and appropriate manner. Always in

Table 3. Comparative review of decision support systems for the stewardship and monitoring of health care-associated infections

Product	Main purpose	EHR/HIS Integration	Real-time alerts / AMS	Customisation	Evidence of impact
LUMED® (APSS/ZIN) (bioMérieux)	CDSS for AMS + HAI Surveillance	High integration with EHR + LIS	Prioritised alerts for ASP teams. APSS module: antimicrobial use optimisation. ZINC module: infection prevention and control.	High local adaptability (integration into local guidelines)	Documented in institutions (supported by bioMérieux®)
TheraDoc / Premier clinical surveillance	Automated infection surveillance + pharmacy/AMS	Very good EHR integration	Real-time alerts for pharmacy and IPC (Infection preventionists)	High customisation	Studies showing cost savings and increased pharmaceutical intervention
iAST® (Pragmatech AI solutions)	Private company software using AI predictive algorithms to improve antimicrobial prescribing (web-based tool)	Good EHR + LIS + hospital formulary integration (robust calculation engine)	Prioritised alerts for ASP teams (based on clinical variables and hospital context)	Moderate local adaptability (predicts probability of success for each antibiotic)	Early documentation in institutions (supported by Pragmatech); impact on empirical treatment
WHONET	Free Microbiology / AMR software	Imports laboratory data	No automated clinical alerts	Medium (configurable for laboratory use)	Global reference for AMR and resistance data (regional/ global)
NHSN (CDC)	National platform for HAI reporting and benchmarking	Integration of aggregated data	Not an operational CDSS	Low (national standard)	National surveillance standard in the USA

CDSS: Clinical Decision Support Systems; AMS: Antimicrobial Stewardship; AMR: antimicrobial resistance; HAI: healthcare-associated infections; EHR: electronic health records; LIS: Laboratory Information Systems; ASP: Antimicrobial Prescribing and Optimisation Support; IPC: infection control practices.

line with this drive for effectiveness that we are calling for here, (using all available scientific information, facilitating responsible prescribing without external obstacles, producing guidelines and protocols that are constantly updated and incorporating new developments in real time, etc.).

d. **Recognising the value of new information technologies**: Currently, within our national framework, a range of digital solutions are already available that enable the optimisation of the selection and use of antimicrobials, support the more efficient management of conventional ASPs, and provide electronic systems to assist with infection and AMR surveillance and control programmes. These include CDSS tools—whether rule-based, predictive model-based or advanced AI-based—ranging from modernised software and apps (WASPSS®, the "MENSA" Guide to Antimicrobial Therapy®, the SNS® Antimicrobial Therapy Guide by AEMPS-PRAN· PROA, Community Infections – Guide to Antibiotic Treatment® from 9 national scientific societies, PROApp by AEMPS-PRAN Ministry of Health) to applications and products generated using artificial intelligence (AI) already available in the healthcare market (iAST® by Pragmatech, InNoCBRsystem3®, Farmatox® by In2AI, TheraDoc/Premier Clinical Surveillance®, WHONET®, NHSN-AU® from the CDC, Epic's EHR 'Bugsy' modules, ARGOS® as a hub for infection surveillance, prevention and control from Quiron Salud and, finally, the highly comprehensive and sophisticated multi-tasking LUMED® in its APSS™ and ZINC™ modules from bioMérieux) (**Table 3**).

C. Proposals for implementing this programme and monitoring its impact on clinical outcomes

C14. Dissemination of the programme to make it operational

The need to make these proposals operational and influential requires a highly active and professional dissemination policy, which could be implemented through initiatives such as the following:

- **Experts** must be involved in horizontal, tree-like and chain-branching training during clinical practice. This could take the form of face-to-face sessions, or as consultations or audits. Consultations or inter-consultations should be considered as opportunities for consultancy.
- **ASPs** should promote, based on the awareness and concept of the ASP-COMPLEX:
  - Specific **audits** to detect and assess the current situation and existing problems
  - Specific informative and audit **clinical sessions**, scheduled across all relevant areas
  - **Collaboration programmes** with regular face-to-face activities involving the departments most affected by these issues (including Emergency Department and Primary Care), to share information on the problems, their assessment, specific proposals for improvement and progress.
  - Specific **training courses** on these aspects.
  - Work with the administration to **integrate the ASP-Complex objectives** into service management agreements, including programme contracts, and into the assessment of compliance with agreed objectives (to help improve them), identifying key objectives that facilitate productive interaction.
  - **Incorporation of the key concepts** of this programme into local clinical guidelines, microbiological maps, electronic prescription systems, the sepsis code programme and other protocols in any format.
  - **Incorporation of new computerised programmes**, information and communication technologies (ICT) or AI-guided systems, which can make the acquisition and transmission of key knowledge more efficient.

C15. Systematic surveillance of improvement initiatives

In order to achieve and consolidate improvements, it is necessary to incorporate **systematic surveillance of optimisation initiatives**. Monitoring is carried out on the basis of indicators, of which there are three types: 1) **Structural**, including the existence of the ASP and experts, antibiotic policies, AMR monitoring programmes, guidelines, educational programmes, etc.; 2) **Process-related**, including recording of antibiotic prescriptions, 48–72-hour review, adherence to ASP recommendations, guidelines or pre-authorisation processes, frequency of de-escalation, oral-to-IV sequencing, time to initiation of antibiotic therapy, culture sampling prior to treatment initiation, etc.; and 3) **Outcome-related**, including monitoring of antibiotic consumption and expenditure, adverse effects, and, most importantly, clinical outcomes: mortality, cure rates, hospital stays, readmissions) [51, 118-119, 510-511].

Since these are initiatives to improve clinical outcomes, the first requirement is the mortality registry, broken down by Health Areas and Infectious Syndromes, and the analysis of causes of mortality, through ASPs, Mortality committees, etc., and their relationship with antibiotic treatment, including timing, choice of empirical treatment, choice of targeted treatment, whether its efficacy has been assessed in a timely and appropriate manner and whether rescue treatment has been considered, patient vulnerability and the type of infection.

Furthermore, for every optimisation initiative that is successfully implemented, a specific indicator must be added—preferably one focused on clinical outcomes—that correlates with evidence demonstrating benefits in both individual and overall clinical health outcomes, and that enables monitoring, analysis and comparison, both over time within the centre itself, and with other healthcare centres through benchmarking. And this must be done despite the fact that the set of validated indicators for measuring effectiveness is limited [4, 51, 94, 117-119].

The following could serve as potential quality indicators for each of the proposals we have submitted:

A1. Achieving earlier and more widespread diagnosis of severe infection

To measure the **delay in the diagnosis of severe infection**:

- 'Door-to-needle time' or 'time to antibiotics' [121, 123, 178-187, 512-517] – which would measure the time elapsed from the patient's arrival at the Emergency Department until the administration of the first dose of antibiotics.
  - If new diagnostic technologies are available, the 'door-to-diagnosis time', defined as the time between admission to the Emergency

Department and the triggering of an alarm for sepsis or severe/complex infection.

- The incorporation of vulnerability assessment into any protocol for managing severe infection.
- Implementation of an automated system for diagnosis and severity categorisation using AI in place.

A2. Identifying and controlling the source of infection more rapidly

- Control of the focus within < 6 hours (when instrumental or surgical intervention is required) [121, 123, 518-519].
- Verify in clinical records that a systematic and structured search for the focus has been carried out from the moment of diagnosis of the infection.

A3. Achieving an earlier, more comprehensive and accurate microbiological diagnosis

- Availability of continuous microbiological support 24/7").
- Adoption, adaptation and implementation of PRODIM [520-521].
- Availability of an optimised, as defined above, and updated, at least annually, local microbiological map.
- Full and permanent integration of the microbiological map into the local antibiotic therapy guidelines, to ensure that its recommendations remain up to date and validated.
- To measure diagnostic delay:
  - Time to microbiological diagnosis, from the moment samples are received by the Microbiology Laboratory.
  - Time from admission to communication of microbiological result, from admission to Emergency Department until the publication of the microbiological test results.

B4. Immediate initiation of empirical antibiotic therapy

'Door-to-needle time' or 'time to antibiotics' [121, 123, 178-187, 512-517].

B5. Selection of an appropriate, active and effective empirical antibiotic therapy

Success rate of empirical antimicrobial treatment. Success implies that the treatment and the chosen dosage regimen are microbiologically active or effective. This applies to serious infections confirmed by microbiological culture, such as bacteraemia, sepsis and septic shock, endocarditis, meningitis, nosocomial infections, etc. [80, 84-85, 140, 188-205, 522].

B6 to B9. From efficacy to effectiveness: how can we achieve effective treatment or the best possible treatment for this type of patient?

There are no valid indicators that are easy to apply. The assessment of whether an active treatment was the best possible (in terms of choice of drugs, adaptation of PK/PD optimisation to the patient's specific conditions, consideration of the use of combinations or other pathogenic factors other than AMR) must be carried out individually and specifically by experts, which requires time that is usually not available. One could begin by assessing cases of clinical failure or mortality in patients receiving antibiotic therapy. And the indicators to be generated could be based on concepts such as:

- **Appropriateness of targeted treatment**. Was it the most effective? (Appropriateness implies, in patients with infections carrying a high risk of mortality, optimal or maximum available effectiveness or efficacy)
- **Time to effective or most effective treatment available.**

B10. Minimise the ecological impact as much as possible in every prescription

In addition to the standard indicators of antimicrobial consumption, exposure and expenditure, and the evolution of resistance [194, 447]:

- Emergence of resistance during treatment.
- Rate of and time to appropriate de-escalation, with and without microbiological information.
- Rate of and time to appropriate treatment discontinuation.
- Other possible indicators:
  * Use of antimicrobial plasma level monitoring in selected indicated cases.
  * Rate of adherence to or monitoring of local guidelines, or of prescribing protocols integrated into electronic prescribing, or of AI-based CDSS tools, etc.
  * Time to microbiological eradication, defined as the time until blood cultures become negative, or until there is a significant reduction in bacterial load.

B11. Consider rescue therapy at an earlier stage

Time to rescue. Defined as the the time from when treatment failure is defined within 48–72 hours until rescue therapy is initiated.

B12. Assessing the importance of convenience in effectiveness

Rate of missed opportunities to improve effectiveness through the use of modern antimicrobials with optimised PK/PD for improved dosing convenience in specific clinical situations.

B13. Give greater and more effective consideration to the benefits of innovation

Although we do not have validated indicators to assess our ability to incorporate innovation and transfer it to patients, we should add to the monitoring process certain assessment criteria or indicators that can help to drive this forward. Aspects such as the following could be considered:

- Time taken to acquire innovative products. Defined as the time from market launch to availability at each centre, analysing the reasons for the delay, which may include, at more demanding levels, delays by the regulatory agency, difficulties in integrating various hospital programmes into a single system or digital solution based on advanced AI, or delays by the administration in marketing it).
- Analysis of missed opportunities to improve effectiveness due to the unavailability of innovations already on the market, in any scenario (empirical, targeted or rescue treatment, clinical decision-support systems based on digital tools, etc.) and in any difficult-to-treat infection.
- Initiatives to disseminate the potential benefits of the acquired innovation, including dissemination times, from awareness of the new drug, diagnostic technique or operating system to all potential prescribers, users or consultants.
- Acquisition-to-prescription time, defined as the time from when a point a product is acquired and made available until its first use or regular use by the areas or departments involved.
- The time taken for new products and strategies to be incorporated into clinical guidelines, microbiological maps or hospital digital management systems.

4. Conclusions

At a time of great concern regarding trends in morbidity and mortality from infections, and mindful of the limitations of our current approaches to combating them, this document sets out a structured programme of proposals aimed at improving, in the short and medium term, the survival of the most at-risk patients with severe infections (**Figure 9**).

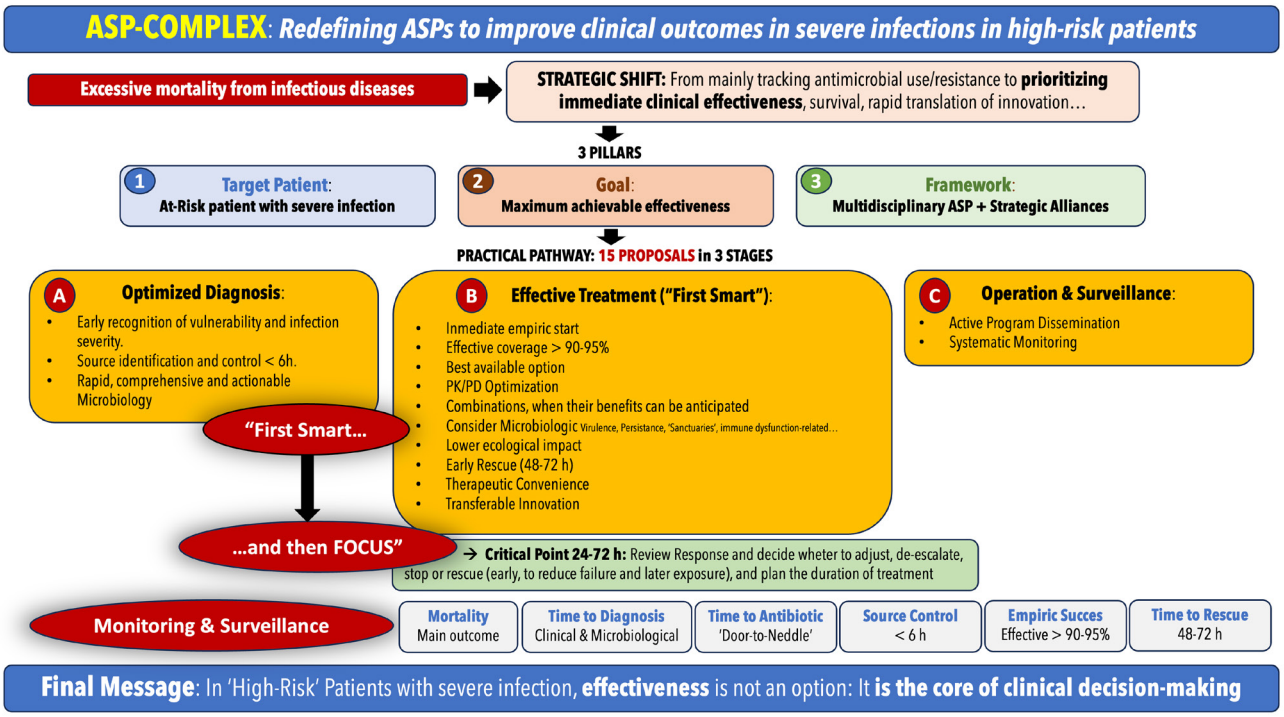

Figure 9. Conceptual and operational summary of the ASP- COMPLEX (a complementary proposal aimed at ASPs and designed to improve the treatment and prognosis of serious infections in high-risk patients).

These are complementary proposals which, on the one hand, reinforce already established initiatives and, on the other, introduce some novel aspects to the approach to this complex problem. They focus on accelerating, standardising, and refining the clinical diagnosis of severe infection and its microbiological diagnosis and, above all, on improving the effectiveness of antimicrobial treatment, based on its immediate initiation with the greatest anticipated effectiveness available, and with an improved capacity to integrate innovation into all stages and processes.

This programme is designed to be implemented within the framework of the antimicrobial stewardship programmes (ASP) (hence the name ASP-COMPLEX), and requires appropriate dissemination and surveillance policies, alongside a collaborative environment among the multiple stakeholders involved in delivering innovation (experts, stewardship teams, healthcare administration, pharmaceutical industry, etc.). In high-risk patients with severe infections, antimicrobial stewardship should not only aim to reduce unnecessary antibiotic exposure, but also to ensure that every patient receives the earliest and most effective treatment possible.

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Conflicts of interest

No commercial, financial, or personal conflicts of interest were identified in relation to the research, authorship, and/or publication of this article.

AI statement

Artificial intelligence tools were used to create Figures 2, 5, and 9. The tools used were Gemini and NotebookLM. All AI-generated content was reviewed, edited and approved by the authors, who take full responsibility for the accuracy, integrity and final content of the figures and the manuscript.

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