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Editorial

The European Association of Urology Guidelines on Urological Infections: Bridging Regulatory Strategy with Proactive Clinical Leadership

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The escalating crisis of *Mycoplasma genitalium* antimicrobial resistance represents a formidable challenge to clinicians worldwide. With macrolide resistance rates in Europe now exceeding 33% and reaching >85% in high-risk populations, the established therapeutic armamentarium has been rendered obsolete [1,2]. The era of single-day azithromycin therapy for urethritis without a precise indication is over. The resistance of this pathogen does more than challenge our treatment strategies: it exposes critical friction between the agility of clinical science and the deliberate pace of public health regulation.

In response to this urgent threat, the European Association of Urology (EAU) guidelines panel on urological infections introduced a paradigm shift in its 2025 recommendations [3]. Grounded in a rigorous analysis of global resistance data, the updated guidelines elevate doxycycline to first-line empiric treatment for non-gonococcal urethritis. Furthermore, the guidelines now recommend a new, extended 4-d azithromycin regimen for confirmed *M. genitalium* infections. This new approach, often implemented as part of a sequential strategy preceded by doxycycline to reduce the initial bacterial load, is designed to optimize pharmacodynamic exposure and minimize selection of resistance, which provides a critical advantage over the now-obsolete single-dose monotherapy [4]. This stance aligns with growing European consensus, as reflected in the new German S3 guideline on penile urethritis, which makes identical recommendations for both doxycycline as first-line therapy and the extended azithromycin regimen as a crucial alternative [5]. This is proactive clinical leadership in action: the translation of emerging evidence into actionable clinical guidance to protect patients and preserve antimicrobial efficacy.

However, this necessary clinical agility operates on a different timeline than the formal regulatory apparatus. The European Medicines Agency (EMA), through its legally mandated pan-EU benefit-risk assessment (Article 31 referral process), concluded a re-evaluation of azithromycin-containing medicinal products for systemic use in May 2025 [6]. On the basis of the evaluation by the Committee for Medicinal Products for Human Use, the European Commission issued a decision making these changes in use applicable in all EU and European Economic Area (EEA) member states in September 2025 [7]. The updated EAU clinical recommendations were disseminated to clinicians in March 2025 [3]. Although both processes occurred in parallel, they were carried out autonomously. The EAU guidelines panel serves as an agile "clinical navigator" and an early warning system designed to provide timely advice for front-line practitioners. Conversely, the EMA acts as the rigorous "regulatory anchor" and undertakes comprehensive evidence-based evaluations, a process that is essential to ensure that conditions of use are legally binding and consistently implemented across the EU/EEA. This regulatory framework allows some degree of alignment with clinical guidelines, as the product information for antimicrobials

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(including azithromycin) specify that consideration should be given to official guidance on the appropriate use of antibacterial agents. While both functions are vital, a lack of coordination and collaboration could create a window of vulnerability.

Antimicrobial resistance is a multidisciplinary public health crisis. We must abandon our siloed thinking. The widespread use of suboptimal azithromycin regimens contributes to selective pressure that transcends individual specialties, as evidenced by a significantly increasing trend of macrolide resistance for invasive *Streptococcus pneumoniae* across Europe according to the European Centre for Disease Prevention and Control [8]. The consequences of our prescribing habits in sexual health are not confined to our clinics; they are felt in pediatric wards and intensive care units across the continent, where macrolides remain a cornerstone for the treatment of respiratory infections.

The time has come to strengthen the synergy between clinical expertise and regulatory authorities. We propose a more formal liaison mechanism, such as a rapid evidence-regulatory interface, between key European guideline panels like the EAU and regulatory bodies like the EMA. Such a framework would allow guideline panels to act as designated "sentinel systems" that officially flag emerging clinical evidence that may warrant regulatory review. Referrals in general allow for stakeholder engagement; however, a well-structured mechanism for regular exchange and interaction between regulators and clinicians, beyond the scope of ongoing referrals, is also welcomed. This would not replace the robust scientific evaluation and regulatory oversight by the EMA but would rather support this role by ensuring that regulatory decisions for authorized antibacterial agents are well informed. In parallel, such collaboration would facilitate timely dissemination of outcomes from such evaluations to relevant guideline panels and health care professionals. Collectively, such actions would facilitate a unified and responsive front in the escalating war against antimicrobial resistance.

Conflicts of interest: The authors have nothing to disclose.

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