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ANTIBIOTIC STEWARDSHIP GAPS AT ADULT-ED:

DETERMINANTS AND PREDICTORS OF INAPPROPRIATE PRESCRIBING AT DISCHARGE (I-PAD STUDY)

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SOMMARIO

ABSTRACT

BACKGROUND

Inappropriate antibiotic prescribing at Emergency Department (ED) discharge remains a major antimicrobial stewardship (AMS) challenge, with reported rates exceeding 50% and important implications for patient safety and antimicrobial resistance. Community-acquired pneumonia (CAP), uncomplicated urinary tract infections (uUTIs/cystitis), and erysipelas/cellulitis are among the most common infectious syndromes managed with oral antibiotics after ED discharge, yet adherence to guideline-recommended therapy remains highly variable. This study aimed to evaluate the appropriateness of antibiotic prescribing for these syndromes and to identify independent predictors of inappropriate prescribing and ED reattendance.

METHODS

We conducted a retrospective observational study including all adult patients discharged from the ED of the University Hospital of Modena between 1 January 2024 and 21 January 2025 with an oral antibiotic prescription. Analyses focused on CAP, cystitis, and mild erysipelas/cellulitis. Prescriptions were assessed according to predefined guideline-based criteria including indication, antibiotic selection, dosage, and treatment duration. Multivariate logistic regression models were developed to identify independent predictors of (I) guideline-discordant prescribing and (II) ED reattendance, adjusting for demographic, clinical, laboratory, microbiological, and therapeutic variables.

RESULTS

Among 30,715 ED discharges, approximately 13% received oral antibiotic therapy. Overall, 2,156 prescriptions (54%) were considered inappropriate according to predefined clinical criteria. Of the 1,837 prescriptions deemed

appropriate regarding indication, 1,230 (67%) involved the target syndromes and constituted the study cohort.

Overall guideline adherence within the target syndromes cohort was 40.8%, with substantial variability across conditions. Erysipelas/cellulitis showed the highest adherence rate (72.0%), followed by CAP (39.5%) and cystitis (31.3%). Inappropriate treatment duration represented the most frequent cause of non-adherence, with guideline-concordant duration observed in 96.2% of adherent prescriptions compared with 31.2% of non-adherent prescriptions. CAP was characterized by frequent use of combination therapy, whereas cystitis showed the lowest adherence regarding antibiotic selection.

In the multivariate model evaluating prescribing appropriateness, male sex (aOR 1.49, 95% CI 1.12–1.98), higher CRP values (aOR 1.02 per mg/dL, 95% CI 1.00–1.05), cephalosporin use (aOR 7.40, 95% CI 3.88–14.11), and combination therapy (aOR 1.62, 95% CI 1.06–2.48) were independently associated with inappropriate prescribing. Conversely, erysipelas/cellulitis (aOR 0.25, 95% CI 0.15–0.40), CAP (aOR 0.61, 95% CI 0.41–0.89), and amoxicillin-clavulanate use (aOR 0.61, 95% CI 0.42–0.86) were independently associated with guideline-concordant prescribing.

During follow-up, ED reattendance occurred in 11.7% of patients, while infection-related mortality was 5.4%. Although overall prescribing appropriateness was not associated with ED reattendance in univariate analyses, cephalosporin use and inappropriate treatment duration emerged as independent predictors of ED reattendance in the multivariate model. Inappropriate combination therapy was also more frequently observed among patients requiring subsequent ED evaluation.

CONCLUSIONS

More than half of antibiotic prescriptions issued at ED discharge were inappropriate, with substantial variability across infectious syndromes. Erysipelas/cellulitis showed the highest level of guideline adherence, whereas CAP and particularly cystitis represented the main areas of suboptimal prescribing. Across two independent multivariate models, cephalosporin use emerged as the strongest and most consistent predictor of both inappropriate prescribing and ED reattendance. AMS interventions targeting cephalosporin overuse, treatment duration, and syndrome-specific prescribing pathways may substantially improve the quality of antibiotic prescribing at ED discharge.

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INTRODUCTION

1. AMS DEFINITIONS

Antibiotics have profoundly shaped the progress of medicine throughout the 20th century, enabling the effective treatment of infectious diseases. Today, they rank among the most prescribed medications in both community and hospital settings. However, their extensive, and sometimes inappropriate use, has contributed to a stable rise in resistant microorganisms. [1]

These resistant organisms constitute a serious public health threat, leading to increased morbidity and mortality associated with infections, as well as higher healthcare costs. For this reason, it is essential to promote good practices in the rational use of antibiotics among healthcare professionals. This objective can be achieved through the implementation of targeted programs and strategies designed to guide clinicians in selecting the most appropriate antibiotic therapy. [1]

The World Health Organization defines antimicrobial stewardship as "a coherent set of integrated actions which promote the responsible and appropriate use of antimicrobials to help improve patient outcomes across the continuum of care". This definition includes diagnostic directed antimicrobial therapy, giving the right antimicrobial agent for the right pathogen-disease combination, and delivering precision dosing. [2]

The goal of antimicrobial stewardship is to improve patient care and health care outcomes. This includes not only limiting inappropriate use but also optimizing antimicrobial selection, dosing, route, and duration of therapy to maximize clinical cure or prevention of infection while limiting unintended consequences, such as the emergence of resistance, adverse drug events, and cost. [3] Benefits of antibiotic stewardship include improved patient outcomes, reduced adverse events including *Clostridium difficile* infection, improvement in rates of antibiotic susceptibilities to targeted antibiotics, and optimization of resource utilization across the continuum of care. [4]

The need for antimicrobial stewardship has been recognized as critical given that up to 50% of antimicrobial use is inappropriate, adding considerable cost to patient care, and that inappropriate and unnecessary antimicrobial use leads to increased selection of resistant pathogens. [3]

2. ASSOCIATION BETWEEN ANTIMICROBIAL USE AND RESISTANCE

Antimicrobial use is the primary driver of antimicrobial resistance (AMR). The relationship is well established: antibiotic exposure provides resistant bacteria with a selective advantage over susceptible strains, leading to increased prevalence of resistance at both individual and population levels. [5] [6] [7]

Up to 50% of antimicrobial prescriptions in human medicine are considered unnecessary, representing a major and potentially modifiable driver of resistance [5]. Over the past two decades, global antimicrobial use has increased by 46% [5] [8]. As a matter of fact, studies indicate that between 20% and 50% of antibiotics prescribed in acute-care hospitals are either unnecessary or inappropriate. [9]

While the link between antimicrobial use and resistance appears logical, the association is complex and influenced by multiple confounding factors including pathogen-drug interactions, mutation rates, emergence of resistant clones, transmission rates between humans and animals, cross-resistance, co-resistance to unrelated drugs, vaccine uptake, healthcare systems, migration, sanitation, and population density. [5]

Antimicrobials drive resistance through selective pressure that provides resistant microbes with a survival advantage over sensitive ones. [8] This occurs through several mechanisms like treatment of infections caused by resistant pathogens, colonizing bacteria exposed to antibiotics prescribed for unrelated conditions and more. [10] Bacteria develop resistance by reducing antibiotic influx, elevating antibiotic efflux, altering cellular targets of antibiotics. [11] Resistance genes then can be spread vertically and horizontally through transformation, transduction and conjugation. [12]

Mathematical models and empirical evidence support that reducing antimicrobial exposure can decrease resistance, though the relationship is complex and varies by organism. [5] [10] A meta-analysis also found that each additional day of antibiotic treatment is associated with a 7% absolute increase in risk of resistance carriage. [13]

Antimicrobial stewardship programs significantly reduce resistance burden, in fact it has been found that these programs reduced infections and colonization with multidrug-resistant Gram-negative bacteria by 51%, ESBL-producing Gram-negative bacteria by 48%, MRSA by 37%, and C. difficile infections by 32%. [14] .

Effects of reducing antibiotic use may require years to manifest. Studies suggest that decreasing prescribing might require up to a decade to substantially reduce corresponding resistance. [15]

3. INTERNATIONAL AND NATIONAL GUIDELINES ON AMS IN HOSPITAL SETTING

National action plans to fight antimicrobial resistance are being used in many countries. Antimicrobial stewardship is an important part of these plans. In hospitals, antimicrobial stewardship programs aim to improve how antibiotics are used, improve patient outcomes, and reduce the spread of resistant bacteria. They do this by creating guidelines, checking prescriptions, and training healthcare staff. [16]

An ASP programme typically consists of three components:

1. System Prerequisites (Structures): these need to be in place before implementation and include the availability of guidelines, the presence of an AMS team, adequate diagnostic capacity, and sufficient human and IT resources.
2. Process Improvement Goals: the AMS team should clearly identify the processes to be targeted, such as providing recommendations for appropriate antibiotic use at the patient level and ensuring that treatment duration is consistent with established guidelines.
3. Improvement Strategies: the AMS team is expected to design and adapt strategies to reach the defined goals based on identified needs and challenges. These may include interventions at both the professional and institutional level, such as audit and feedback or educational activities. [17]

Based on the results of the systematic review by Rennert-May et al [18] , the use of the National Institute for Health and Care Excellence (NICE) guideline or the Infectious Diseases Society of America and the Society for Healthcare

Epidemiology of America (IDSA/SHEA) guideline is recommended for the development and implementation of a hospital-based ASP. [19] [4]

4. ANTIMICROBIAL STEWARDSHIP IN THE EMERGENCY DEPARTMENT

The ED is frequently the primary entry point into the hospital and a primary location for acute clinical encounters. Infection is one of the most common reasons for which patients seek acute unscheduled care. The Centers for Disease Control and Prevention (CDC) estimate that approximately 11% (16 million) of annual U.S. emergency department diagnosis groups are attributable to infection. [20]

Since infections are among the most common causes of emergency room visits antimicrobials are one of the most prescribed drug classes in the ED. [20]

The CDC estimates that in 2015 US EDs produced over 28 million antibiotic prescriptions. Although data specific to overall ED antibiotic prescribing appropriateness is lacking, a recent single center study in a Veterans Affairs hospital ED identified that 39% of all antimicrobial use was inappropriate. [20]

Antimicrobial therapy in the emergency department is typically initiated empirically, requiring rapid clinical decision-making often in the absence of microbiological data or outcome feedback. Rates of inappropriate antibiotic use in this setting are comparable to inpatient care, estimated at approximately 40–60%. This level of inappropriateness is concerning, particularly given that full adherence to prescribing guidelines has been associated with reduced mortality. [21]

4.1 ESSENTIAL ELEMENTS OF ANTIMICROBIAL STEWARDSHIP IN ED

ED antimicrobial stewardship programs should target these fundamental processes:

- Make a (tentative) clinical diagnosis: The initial assessment is fundamental to guide appropriate antimicrobial selection.
- Starting empirical therapy following guidelines indications.
- Following up discharged patients: ensuring culture review and eventual antibiotic adjustment for the patient sent home from ED. [21]

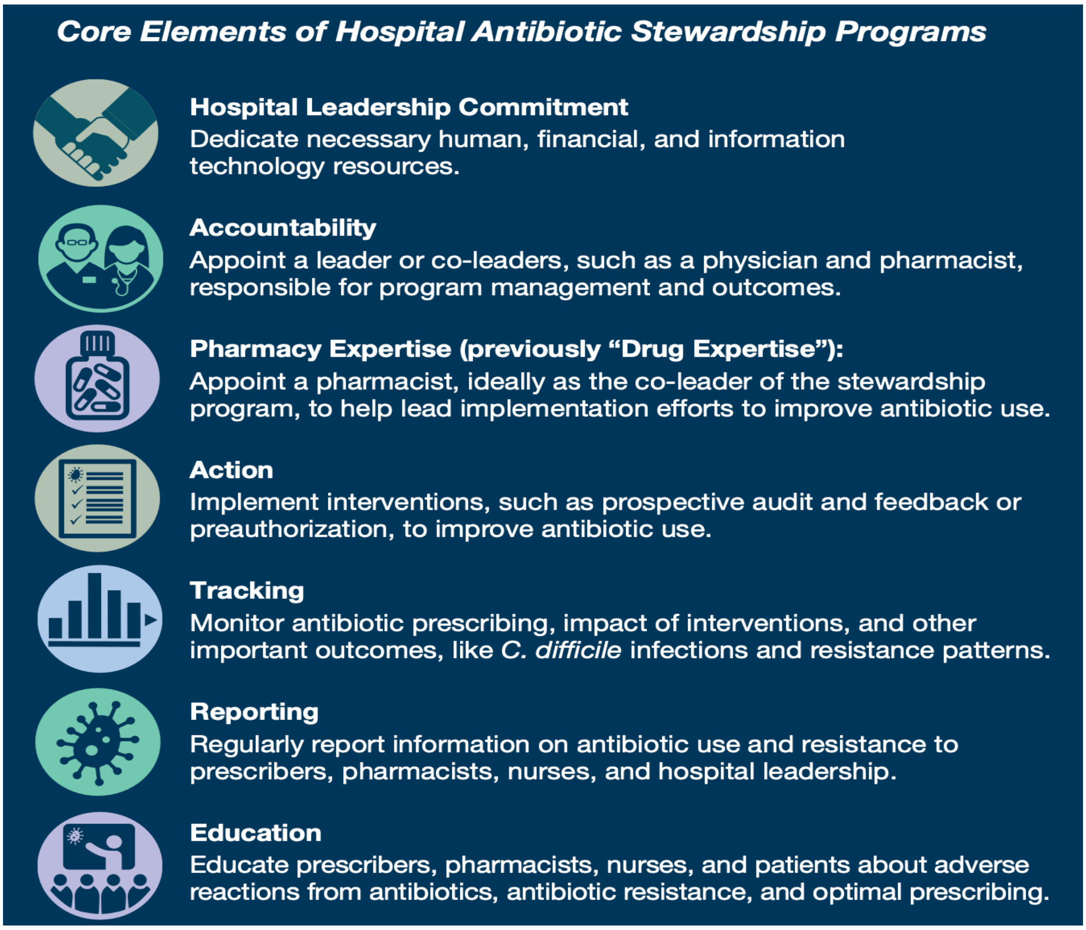
Appropriate antibiotic selection requires choosing the optimal drug regimen based on the suspected pathogen, local resistance patterns, patient factors, and antimicrobial stewardship principles, for example specifically selecting narrow spectrum agents when possible. [4] [22]

The timing of administration of antibiotic is also fundamental, especially in the ED department: for septic shock, antibiotic should be administered immediately in the ED, ideally within 1 hour of recognition, for sepsis without septic shock timing depends on certainty, with a 3-hour window for assessment when diagnosis is uncertain. [23]

Shorter antibiotic courses (less than 7 days) are as effective as longer courses for most common infections treated in the ED , reducing adverse events and resistance. [24]

Essential element for AMS in the ED is also the use of diagnostic testing like rapid diagnostic test and molecular diagnostic: Procalcitonin is useful for guiding antibiotic discontinuation but not recommended for initiation decision in the ED setting. [25] Rapid diagnostic testing alone without stewardship involvement shows limited benefit, but reduces time to appropriate therapy from 24 hours to 5-6 hours. [4]

In 2019, Centers for Disease Control and Prevention (CDC) updated the hospital Core Elements, applicable in all hospitals, regardless of size, as shown in the image below. [26]



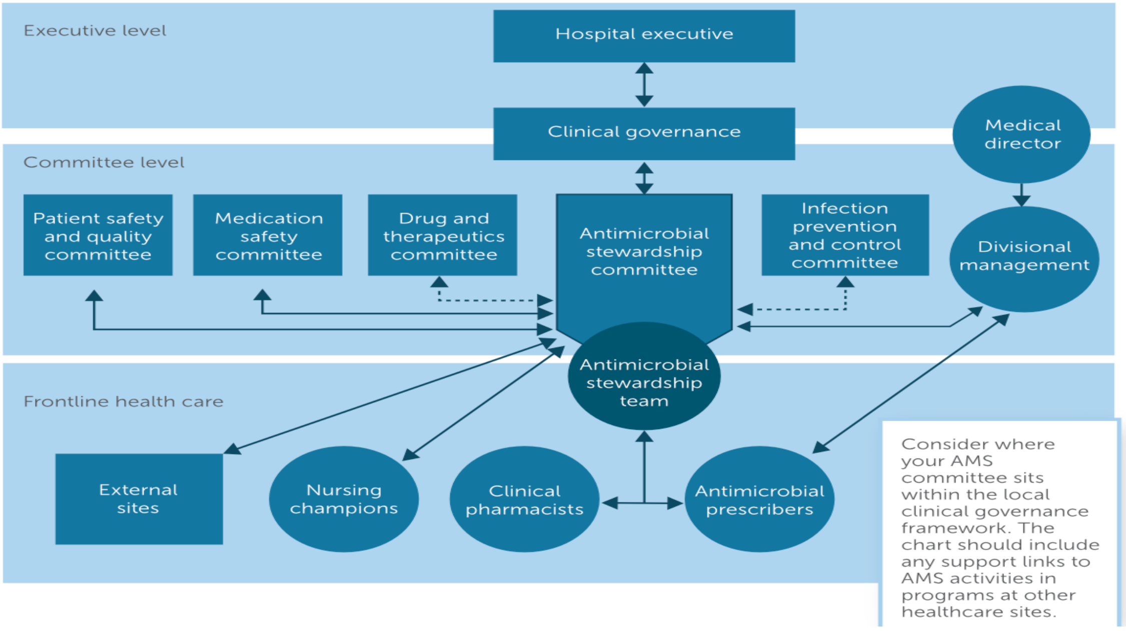
Core Elements of Hospital Antibiotic Stewardship Programs, adapted from CDC

4.2 STRUCTURE AND GOVERNANCE OF AMS PROGRAMS IN ED

Effective antimicrobial stewardship programs in the emergency department need a team of different healthcare professionals working together. The structure should be designed for the special challenges of the ED, such as many patients, limited time, uncertainty in diagnosis, and the ED's role between outpatient and inpatient care. [27] [21]

The core stewardship team should include an infectious diseases physician but also a clinical pharmacist with ID training**,** and additional support from a clinical microbiologist, information systems specialist, infection control professional, and hospital epidemiologist. [3]

The emergency department has unique governance challenges compared to inpatient settings, so the standard antimicrobial stewardship model needs to be adapted. In this context, emergency doctors should take the lead in stewardship activities, with support from infectious disease specialists, as this approach has been shown to reduce the use of certain antibiotics [28]. The presence of a pharmacist in or linked to the ED is also very important, since research shows that pharmacists improve appropriate antibiotic use and help patients receive the right treatment more quickly [29]. Close collaboration with infectious disease specialists remains essential, as they contribute to guideline development, interpretation of resistance data, and management of complex cases [27] .At the same time, nurses and other healthcare professionals play a key role by ensuring proper sample collection before antibiotics are given and by educating patients when they are discharged.



Example of a governance structure for a hospital antimicrobial stewardship program, adapted from Australian Commission on Safety and Quality in Health Care. Antimicrobial Stewardship in Australian Health Care. Sydney: ACSQHC; 2023

The ED needs flexible and multi-approach strategies instead of strict prior-authorization models used in hospitals. One important idea is to use simple clinical pathways and guidelines for common infections like pneumonia, urinary tract infections, and skin infections, based on local antibiotic resistance data. [21] Another key strategy is prospective audit and feedback, which means reviewing how antibiotics are prescribed and giving feedback to clinicians [3]; in the ED this is often done after the visit, for example by checking charts later. It is also very important to review microbiology culture results and follow up with patients who have been discharged, because this helps make sure they are on the right treatment even after they leave the ED. [21]

An international Delphi consensus identified 22 quality indicators for antimicrobial stewardship in the emergency department, grouped into five key domains. These indicators aim to enhance the quality of care by promoting the responsible and effective use of antibiotics, particularly in the fast-paced environment of the ED.

The first domain, "Stewardship Prerequisites," emphasizes the need for essential resources, such as local guidelines that are regularly updated, antibiograms that provide information on local resistance patterns, and designated stewardship personnel responsible for overseeing AMS activities in the ED.

The second domain focuses on "Diagnostics," ensuring that microbiological testing is done before starting empirical antibiotic therapy. This allows for a more targeted approach, ensuring that antibiotics are used appropriately and only when needed.

The third domain, "Empirical Treatment," stresses the importance of aligning empirical therapy with established guidelines, using antibiotics with the narrowest possible spectrum to reduce resistance, and administering treatment as quickly as possible, especially for critically ill patients.

The fourth domain is "Documentation," which highlights the need for thorough and clear record-keeping. This includes documenting the reason for antibiotic selection, specifying the planned duration of therapy, and having a clear plan for reassessing the treatment based on patient response and microbiological results.

Finally, the "Patient Discharge" domain focuses on ensuring that patients discharged from the ED receive appropriate antibiotic prescriptions, when necessary, as well as clear follow-up instructions, including any further tests, consultations, or adjustments to the treatment plan. [30]

In summary, these quality indicators are designed to optimize antimicrobial stewardship in the ED, improve patient outcomes, and reduce the risk of antibiotic resistance by ensuring that antibiotics are prescribed and managed thoughtfully and effectively. [30]

In Italy, the governance of antimicrobial stewardship works through a system with several levels, starting from the national level (PNCAR) and moving down to regional authorities and individual hospitals, including their emergency departments. One of the main challenges is the significant differences between regions, especially between Northern and Southern Italy. [31] [32]

Italy launched its National Plan for the Control of Antibiotic Resistance (PNCAR) in 2017, which was updated in 2022. It follows a "One Health" approach and is aligned with European Union recommendations after an important evaluation by the ECDC [31] [33].

The plan is organized into seven main areas: governance, surveillance and monitoring, appropriate use of antibiotics, prevention and control of healthcare-associated infections, education and training, collaboration among stakeholders, and implementation. [34]

To track progress, Italy developed a self-assessment tool called SPiNCAR (Supporto al Piano nazionale per il contrasto all'antimicrobico resistenza). The first SPiNCAR assessment found high implementation levels in governance, surveillance and hospital associated infection prevention. [31]

4.3 AMS IMPLEMENTATION IN THE ED

Implementation of an Antimicrobial Stewardship Program in the Emergency Department requires the translation of stewardship principles into routine clinical practice within a high-pressure, time-sensitive environment. [4] Unlike inpatient settings, the Emergency Department is characterized by rapid decision-making, limited diagnostic information, and high patient turnover, all of which significantly influence antimicrobial prescribing behavior. [35]

For this reason, successful implementation relies on integrating concise, evidence-based clinical pathways directly into the clinical workflow. These pathways should be focused on common infectious presentations such as pneumonia, urinary tract infections, skin and soft tissue infections, and sepsis because syndrome-specific pathways is strongly supported by the literature. The IDSA/SHEA guidelines recommend that ASPs implement interventions targeting specific infectious disease syndromes because the message can be focused, clinical guidelines reinforced, and sustainability improved. [4] A systematic review of 43 ED AMS studies confirmed that guideline and clinical pathway implementation was one of the two most commonly reported intervention types, with benefits primarily including improved delivery of care and decreased antimicrobial utilization. [36]

The four most commonly targeted syndromes in ED AMS programs as said before are:

- **Community-acquired pneumonia (CAP)**: Clinical pathways have demonstrated improved guideline-concordant prescribing and reduced broad-spectrum use [21]
- **Urinary tract infections (UTI):** Including reduction of treatment for asymptomatic bacteriuria, a major driver of unnecessary antibiotic use in the ED [21] [27]

- **Skin and soft tissue infections (SSTI):** Pathways targeting appropriate narrowing from IV to oral therapy and avoidance of unnecessary MRSA coverage [36]
- **Sepsis**: for sepsis empirical broad-spectrum therapy is appropriate but requires structured reassessment at 48–72 hours [37]

In addiction the role of Electronic Health Record-based order sets and clinical decision support tools is particularly well-supported for the ED setting. A global meta-analysis found that computerized clinical decision support systems had the largest effect on reducing antibiotic prescriptions among all ASP intervention types studied. [38]

Effective clinical decision support within the Emergency Department should be simple and easy to use during busy shifts in the ED. This includes the use of pre-populated, syndrome-specific antibiotic order sets that are aligned with local resistance patterns and antibiograms, ensuring that empiric therapy reflects current epidemiology. Decision support systems should also incorporate allergy-aware prescribing prompts to reduce the risk of adverse reactions, as well as automated dose adjustments based on renal function to improve safety and accuracy. In addition, embedding default durations of therapy helps prevent unnecessarily prolonged treatment courses. Finally, integrated alerts for post-discharge culture results enable timely follow-up and optimization of antimicrobial therapy, particularly for patients who have already left the Emergency Department. [4] [21] [39]

4.4 STEWARDSHIP METRICS AND TARGETS IN ED

Measuring the impact of an Antimicrobial Stewardship Program in the Emergency Department requires a clear and organized way to evaluate results. It is important to look at both how antibiotics are used and whether patient care remains safe. For this reason, metrics are usually grouped into three main categories.

The first group includes **antimicrobial use (consumption) metrics**, which show how often and what types of antibiotics are prescribed.

The second group consists of **quality or process indicators**, which assess whether prescribing follows recommended guidelines and best practices.

The third group includes **safety metrics**, which ensure that reducing antibiotic use does not negatively affect patient outcomes, like as increasing return visits or treatment failures.

First of all, a way to measure how much antibiotics are used is called days of therapy (DOT)**.** This means counting how many different antibiotics a patient receives each day. DOT is widely used in the United States because it is simple and not affected by differences in dosing [40] [41]. The Centers for Disease Control and Prevention also uses a similar measure, reported as antimicrobial days per 1,000 patient-days, as a standard way to track antibiotic use. [41]

However, DOT has some important limits, especially in the Emergency Department. It does not include antibiotics that are prescribed when patients are discharged, so it may not show the full picture of antibiotic use in this setting. It is also influenced by how long patients stay in the hospital. [40]Another limitation is that DOT does not consider how broad or strong an antibiotic is. For example, one day of a very broad spectrum antibiotic like meropenem counts the same as one day of a narrower treatment, even though their impact on resistance can be very different. [40]

To solve this problem, newer measures have been developed, such as days of antibiotic spectrum coverage (DASC) and the antibiotic spectrum index (ASI). These metrics consider how broad the antibiotic activity is. Studies have shown that they give different information compared to DOT, so they are useful when used together. For a more complete evaluation of antibiotic use, it is recommended to combine DOT with one of these newer measures. [42]

In the Emergency Department, it is also important to look at outpatient prescribing. Useful measures include evaluating the number of antibiotic prescriptions per 1,000 visits, the percentage of visits where at the end an antibiotic is prescribed, and prescribing rates for specific conditions. [40] [43]

The most comprehensive ED-specific quality indicator framework comes from the Schoffelen et al. Delphi study, which developed 22 quality indicators (QIs) across five domains (as shown before) [30]:

Domain	**Number of QIs**	**Examples**	**References**
Stewardship prerequisites	6	Availability of local guidelines, antibiogram access, AMS team involvement	[40]
Diagnostics	1	Blood cultures obtained before antibiotic administration	[40]
Empirical treatment	10	Guideline-concordant empirical therapy, appropriate spectrum, timely administration	[40]
Documentation	4	Documented indication for antibiotic, planned duration, reassessment plan	[40]

Domain	Number of QIs	Examples	References
Patient discharge	1	Appropriate discharge antibiotic prescription with documented duration	[40]

A Delphi consensus by Moehring et al. identified six key metrics for antimicrobial stewardship in acute care. These metrics scored highly in four areas: improving prescribing, improving patient care, helping target interventions, and being practical to use. The six metrics are:

- *C. difficile* incidence per 10,000 patient-days,
- *C. difficile* incidence per 1,000 admissions
- Incidence of drug-resistant pathogens
- DOT per admission
- DOT per patient-days
- Redundant therapy events. [44]

Other process metrics commonly used also include indicators like the guideline-concordant prescribing rate or the unnecessary prescribing rate. Galanter et al. showed that using an empiric therapy guide improved appropriate prescribing, with 90.5% of prescribers reaching at least 75% adherence to guidelines. Buehrle et al. evaluated prescriptions where antibiotics were not indicated and found that these decreased from 55.6% to 38.7% after a peer comparison intervention. [45] [43]

The third group includes safety metrics, which are used to make sure that antimicrobial stewardship (AMS) interventions do not harm patients. These are important for demonstrating program safety and receive clinician support. Some important safety outcomes are :

- **Mortality:** In the 4-year Verona ED antimicrobial stewardship study, mortality did not increase even though antibiotic use was reduced. In contrast, the Italian study by Monari et al. showed a significant decrease in mortality after the implementation of AMS programs. [46] [47]
- **C. difficile infection (CDI):** This is considered one of the most important balancing metrics by experts. The Verona study showed a significant reduction in CDI incidence over time. [44] [46]
- **Length of stay:** The Verona study also reported a small but consistent reduction in hospital length of stay across medical wards. [46]
- **Repeat ED visits:** Studies on pharmacist-led AMS programs showed that repeat visits to the ED for the same complaint did not significantly increase, confirming the safety of these interventions. This was also supported by the meta-analysis by Kooda et al. [29]
- **Multidrug-resistant organism (MDRO) bloodstream infections:** The study by Monari et al. found no significant increase in infections caused by resistant gram-positive bacteria, gram-negative bacteria, or Candida during the intervention period. [47]
- **30-day readmission rate** was identified as an important clinical outcome measure in a Canadian pediatric antimicrobial stewardship Delphi consensus. [48]

Setting realistic targets based on evidence is important to guide antimicrobial stewardship efforts in the Emergency Department and to show their value to hospital leadership. These targets come from published studies and can be grouped into four main areas: improving prescribing quality, reducing antibiotic use, optimizing treatment for specific conditions, and ensuring patient safety.

Prescribing Quality Targets are:

Metric	Baseline (Pre-Intervention)	Demonstrated Achievable Target	Intervention Type	References
Guideline-concordant prescribing	40–63%	**≥75–84%**	Empiric therapy guide; multifaceted UTI intervention	[45] [49]
Overall optimal prescribing (correct agent + dose + duration)	8–22%	**23–29%**	Indication-based order sentences; peer comparison	[43] [50]
Unnecessary antibiotic prescriptions	56%	**≤39%** (30% relative reduction)	Peer comparison with monthly feedback	[43]
Appropriate prescribing (pharmacist-led)	Standard care	**OR 3.47** (95% CI 2.39–5.03) improvement	Pharmacist-led AMS (meta-analysis, 22 studies)	[29]
Broad-spectrum antibiotic use	Baseline rate	**13.6% absolute reduction**	Empiric therapy guide	[45]

Syndrome-specific metrics are also one of the most important ones because they allow focused measurement on very frequent conditions like UTI , CAP, Skin and soft tissue infections and other respiratory infections. Prioritize high-impact, high-volume syndromes is significant because they account for the majority of ED antibiotic prescriptions and offer the greatest opportunity for measurable improvement. [21]

4.5 BARRIERS TO OPTIMAL PRESCRIBING AT ED DISCHARGE

There are many barriers that make it difficult to prescribe antibiotics correctly at discharge from the emergency department. These barriers can be related to the hospital organization, healthcare professionals, patients, or the healthcare system. About one-third of antibiotics prescribed in the ED are inappropriate, and one of the most common issues is that antibiotics are prescribed for too many days. [51]

The period between patient observation and discharge is particularly important because doctors are often unsure about the patient's future clinical course or follow-up care. [52] Most antimicrobial stewardship programs mainly focus on hospitalized patients, so the ED is often neglected even though inappropriate antibiotic use is also very common there. [21] Many hospitals do not have stewardship strategies specifically designed for discharge prescriptions, even if these interventions are very effective in reducing unnecessary antibiotic use.

Communication problems during transitions of care, especially with outpatient doctors and nursing facilities, also make it harder to optimize antibiotic prescriptions at discharge. In addition, it is often difficult to measure and monitor antibiotic prescribing at discharge, which limits quality improvement efforts. [53]

Diagnostic uncertainty is among the most common reason of inappropriate prescribing. Physicians rely on clinical judgment but often prescribe antibiotics when uncertain about diagnoses, particularly for immunocompromised or elderly patients with comorbidities. [54]

Limited knowledge and poor familiarity with guidelines can contribute to inappropriate antibiotic prescribing. Physicians may also rely too much on diagnostic tests to justify prescribing antibiotics instead of focusing on treating symptoms. [55] [56] Another important factor is the perceived expectation from patients to receive antibiotics. This can lead to unnecessary prescribing, especially when physicians are working under time pressure. In the ED environment, doctors often feel pressured to prescribe antibiotics when patients ask for them, because there is limited time to build rapport or explain why antibiotics may not be necessary. [56] [54] [57]

Common patterns of inappropriate prescribing include prescribing antibiotics when they are not necessary, using them for too many days, choosing antibiotics that could be avoided, and prescribing the wrong dose or frequency. [43] [58] [59]

One study found that more than half of antibiotic prescriptions (55.6%) were unnecessary because antibiotics were not indicated at all. [43] Another important problem is excessive treatment duration. This is one of the major contributor to inappropriate prescribing, with a mean of 40% of total antibiotic therapy administered post-discharge. Fluoroquinolones are also frequently overused, even if they are associated with important safety warnings. Some studies reported that only about 25% of fluoroquinolone prescriptions were actually appropriate. [58] In addition, prescribing errors involving the wrong dose, strength, or administration frequency account for 58.5% of all identified errors. [59]

5. ANTIMICROBIAL STEWARDSHIP PROGRAMS AND INTERVENTIONS IN ED

Strategies and tools for antimicrobial stewardship

Effective antimicrobial stewardship programs in the emergency department use different strategies to improve antibiotic prescribing despite challenges such as limited time and diagnostic uncertainty. Common interventions include audit and feedback, pharmacist support, clinical guidelines, and decision support tools. [21] [29] [36] [4]
Studies show that these programs reduce inappropriate antibiotic use and improve prescribing quality without affecting patient safety. [29] [46] [43]

As said before, the four essential processes that constitute the foundation of ED antimicrobial stewardship are [21]:

1. Making a tentative clinical diagnosis of infection.
2. Starting empirical therapy based on that diagnosis.
3. Performing microbiological tests before initiating therapy.
4. Following up patients who are discharged from the ED.

Among the tools we can use there is the computerized decision support system (CDSS) which is a computer tool that gives recommendations during prescribing. They provide real-time treatment recommendations at the point of prescribing. Implementation has been associated with reduced broad-spectrum antibiotic use, improved antibiotic dosing and selection, fewer prescribing errors, reduced adverse events and costs and reduced length of stay and mortality. [4]

Indication-based antibiotic order sentences (AOS) are a simple tool integrated into electronic health records to help clinicians prescribe antibiotics more appropriately. These are pre-made prescriptions connected to a specific infection.

For example, when a doctor selects “urinary tract infection,” the system automatically suggests the recommended antibiotic, dose, and treatment duration according to guidelines. Studies showed that the use of AOS improved optimal prescribing from 8% to 23% for common infections such as uncomplicated respiratory infections, urinary tract infections, and skin infections. [50]

Another important antimicrobial stewardship strategy in the emergency department is the development of evidence-based guidelines and clinical pathways, which are among the most frequently used interventions to improve antibiotic prescribing. [36]

Prospective audit with intervention and feedback represents a core stewardship strategy but is underutilized in the ED setting [36] [60]. Instead, peer comparison-based interventions provide an alternative feedback mechanism well-suited to the ED, which has demonstrated to reduce antibiotic prescriptions. [43]

5.1 DECISION SUPPORT SYSTEMS (PASSIVE VS ACTIVE TOOLS)

Passive and active clinical decision support systems (CDSS) differ fundamentally in how they engage prescribers. Active CDSS automatically triggers alerts or recommendations when specific antibiotics are ordered, requiring prescriber interaction. Passive CDSS provides decision support only when clinicians actively search for it. Active systems that automatically provide decision support are more likely to improve prescribing practice compared to systems requiring active initiation by providers. [61] [62]

Regardless of passive versus active design, CDSS implementation demonstrates substantial benefits:

- Appropriate antibiotic therapy is twice as likely with CDSS [63] [64] .
- Mortality reduction from 18% to 15%. [63] [64]
- Reduced broad-spectrum antibiotic use, improved dosing, fewer prescribing errors, reduced adverse events, decreased costs, and shorter length of stay. [4] [65]

CDSS may come in a variety of formats like Knowledge-based systems that operate on predefined rules and clinical guidelines programmed by developers. (These can be delivered through various platforms). [66]

Or they can be like Data-driven systems that employ artificial intelligence and machine learning algorithms that learn patterns from large datasets to generate patient-specific recommendations. [67] These range from simple statistical models to complex deep learning systems. Common delivery platforms encompass:

- printed booklets with treatment recommendations for common infections

- Mobile applications on smartphones and tablets that provide point-of-care access to clinical guidelines, drug calculations, and decision algorithms
- sophisticated computer-based systems embedded in the electronic health record (EHR) that provide real-time alerts, reminders, and treatment recommendations during the prescribing process. [68]

No single CDSS format has been proven definitively superior.

5.2 ELECTRONIC APPROVAL SYSTEMS

Electronic approval systems improve the formulary process by making antibiotic approvals easier for prescribers and pharmacists, while helping the antimicrobial stewardship (AMS) team focus on prescriptions that need further review. These systems also support auditing of antibiotic use and allow targeted feedback to individual doctors, hospital units, and committees. [66]

To implement these systems effectively, close collaboration is needed between pharmacy staff, clinical microbiology, infectious disease specialists, and hospital departments. The system should also be adapted to local guidelines, formularies, and approved indications defined by the AMS or drug and therapeutics committee. Today, pre-prescription approval processes are increasingly included in electronic medication management (EMM) systems, either as independent tools or combined with external electronic antimicrobial approval systems. [67]

Preauthorization is a restrictive strategy requiring clinicians to obtain approval for certain antibiotics before they are prescribed, typically through phone calls or electronic systems to the stewardship team. [4]

The IDSA/SHEA guidelines provide a strong recommendation for preauthorization and prospective audit and feedback as core components of antimicrobial stewardship programs. [4]

Preauthorization has shown important benefits in antimicrobial stewardship programs. Studies reported a 32% reduction in the cost of intravenous antibiotics and an improvement in antimicrobial susceptibility among gram-negative bacteria, including *Pseudomonas aeruginosa*. In ICU patients, susceptibility to imipenem increased from 65% to 83%. These interventions did not negatively affect hospital length of stay, survival, or overall patient outcomes. In addition, preauthorization was found to be more effective than persuasive strategies in reducing *Clostridioides difficile* infections. [4]

Electronic approval systems are available 24 hours a day and help communication between healthcare professionals without slowing clinical workflow. A computerized approval system based on specific indications for restricted antibiotics was associated with lower antibiotic consumption and improved *Pseudomonas* susceptibility over a two-year period [4].

The experience and skills of the person giving approval are very important for the success of antimicrobial stewardship programs. Studies showed that approval by an antimicrobial stewardship team, including a clinical pharmacist and an infectious diseases specialist, was more effective than approval given by fellows during off-hours. It resulted in more appropriate recommendations, higher cure rates, and fewer treatment failures. In addition, direct review of the patient chart was found to be more effective than phone-based communication during the preauthorization process. [4]

5.3 MONITORING ANTIMICROBIAL USE AND EVALUATION OF INTERVENTIONS

Monitoring antimicrobial use in the emergency department is important to evaluate whether stewardship interventions are effective and safe. The IDSA/SHEA guidelines recommend using days of therapy (DOTs) instead of defined daily doses (DDDs) to monitor antibiotic use, together with assessment of adherence to treatment guidelines. Evaluating prescribing appropriateness in the ED is difficult because physicians often prescribe antibiotics before having a confirmed diagnosis, patients have very different clinical presentations, and many are discharged without follow-up data. [30] [4] [21]

Measuring Appropriateness of Prescribing is done by looking at guideline concordance. Studies define appropriateness variably, but usually they classify prescribing as optimal when the correct antibiotic, dose, and duration are prescribed according to guidelines; unnecessary when antibiotics are not indicated; and suboptimal when the wrong drug, dose, or duration is used. [4] [51] [43]

The Medication Appropriateness Index has been adapted for ED antimicrobial prescribing assessment, evaluating indication, effectiveness, dose, directions, duration, drug-drug interactions, and cost-effectiveness. [68]

Most stewardship studies in the ED use before-and-after or interrupted time-series designs to evaluate interventions. Monitoring should also include balancing measures such as mortality, readmissions, treatment failures, adverse events, and length of stay to ensure that interventions do not negatively affect patient care. [36] [43] [46]

Before starting an intervention, it is important to evaluate baseline prescribing patterns, local resistance data, and current guideline compliance. [21] [36]

Interventions can target specific infections such as urinary tract infections, pneumonia, or skin infections, or they can focus on overall prescribing behavior. [50] [69]

Electronic health records, pharmacy databases, and clinical decision support systems are commonly used to collect prescribing data, although manual chart review is often still needed to assess appropriateness. Long-term monitoring is necessary to evaluate whether improvements are maintained over time and to identify possible regression or intervention fatigue. [46] [70] [71] [72]

An additional challenge is that around 40% of antibiotic therapy occurs after discharge. For these patients, it is often difficult to know whether prescriptions were completed, whether treatment was changed after culture results, or whether adverse outcomes occurred in other healthcare settings. High patient turnover and the variety of clinical presentations in the ED also make comprehensive monitoring more complex and resource-intensive. [53] [73] [30] [21]

6. INFECTIOUS SYNDROME–SPECIFIC ANALYSIS AND STEWARDSHIP IMPLICATIONS

6.1 Respiratory tract infections and community-acquired pneumonia (cap)

Community-acquired pneumonia (CAP) is among the most common infections managed in the emergency department, making it an important focus for antimicrobial stewardship interventions.
According to an invited review in the New England Journal of Medicine, CAP management requires systematic risk stratification, targeted diagnostics, evidence based antibiotic selection, and appropriate treatment duration. [74]

6.1.1 Risk Stratification

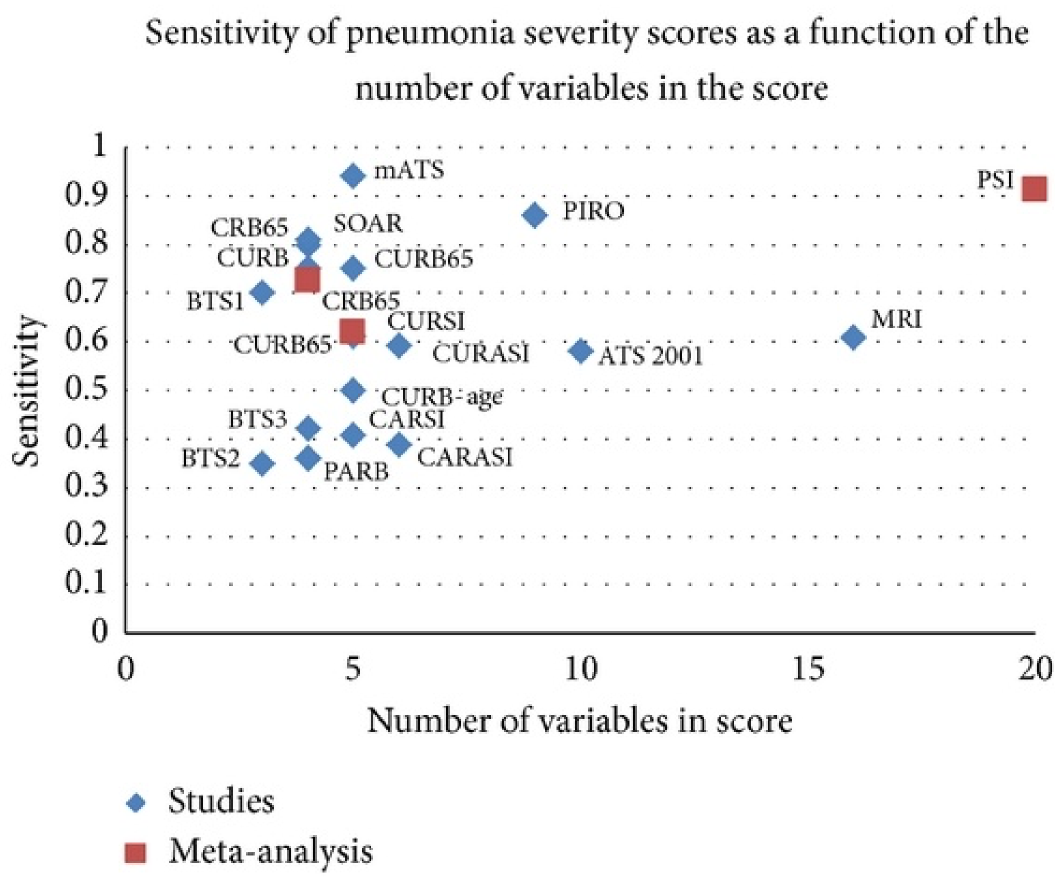
The decision to hospitalize patients with CAP should be based on clinical judgment supplemented by severity scores, with the Pneumonia Severity Index (PSI) and CURB-65 being the most commonly used tools. The PSI divides patients into five risk categories (I-V), with calculations based on patient demographic and clinical variables originally developed to predict 30 day mortality. [74]

Outpatient treatment is recommended for patients with CURB-65 scores of 0 or 1, a short hospital stay or close observation should be considered for scores of 2, and hospitalization is recommended for scores of 3 to 5. [74]

The CURB-65 score assigns 1 point each for new onset confusion, blood urea nitrogen greater than 19 mg/dL, respiratory rate greater than 30 breaths per minute, systolic blood pressure less than 90 mm Hg or diastolic blood pressure less than 60 mm Hg, and age 65 years or older. [74]

For patients requiring hospitalization, indications for ICU care include the use of mechanical ventilation and the presence of shock. Severity score thresholds have not been defined for immunocompromised patients, and thresholds for admission should be based on clinical judgment in these populations. [74]

The following figure illustrates that simpler severity scores like CURB-65 achieve sensitivities comparable to more complex systems, suggesting that additional variables do not necessarily translate to superior discriminative ability:



Risk Prediction Models for Mortality in Community-Acquired Pneumonia: A Systematic Review. Biomed Res Int. 30 aprile 2013.

6.1.2 Diagnostic Challenges

The diagnosis of CAP is based on clinical presentation combined with radiographic evidence of pneumonia. While chest radiography remains the standard imaging modality, it has limitations in sensitivity and specificity. The review emphasizes that diagnostic testing should be tailored to severity and clinical context rather than applied universally. [74]

The diagnosis of CAP can be difficult in the emergency department for several reasons. Chest X-rays are not always completely accurate, and radiological findings may appear later than clinical symptoms. In many cases, the causative microorganism is not identified, even after microbiological testing. In addition, CAP can present with signs and symptoms similar to other noninfectious conditions, making diagnosis more complex. Another important challenge is the limited time available in the ED, where physicians often need to make rapid treatment decisions before the full diagnostic evaluation is completed. [75]

6.1.3 Antibiotic Selection

For ambulatory patients younger than 65 years who are otherwise healthy and have not recently received antibiotics, it is recommended the use of one of three oral options: amoxicillin (1 g three times daily), doxycycline (100 mg twice daily), or a macrolide (azithromycin 500 mg on day 1 then 250 mg daily, or clarithromycin 500 mg twice daily). However, macrolides should only be considered in areas where pneumococcal resistance to macrolides is less than 25%. [74]

For patients who have taken antibiotics within the past 3 months, have serious coexisting conditions (chronic heart, lung, kidney, or liver disease; diabetes mellitus; or alcohol dependence), or who are smokers, the recommended regimen is amoxicillin-clavulanate combined with either a macrolide (preferred) or doxycycline. [74]

Patients who cannot take beta-lactam agents due to hypersensitivity or adverse effects can instead be treated with a monotherapy with respiratory fluoroquinolone (levofloxacin 750 mg daily or moxifloxacin 400 mg daily) or one of two more recently approved agents, lefamulin or omadacycline. [74]

The rationale for combination therapy in patients with comorbidities is to provide coverage for both typical bacterial pathogens (particularly Streptococcus pneumoniae and Haemophilus influenzae) and atypical organisms (Mycoplasma pneumoniae, Chlamydophila pneumoniae, Legionella species). The beta-lactam component targets typical bacteria, while the macrolide or doxycycline provides atypical coverage. [74]

Addition of anti-MRSA or anti-Pseudomonas coverage is recommended if risk factors are present and supported by local microbiological data. Risk factors include prior respiratory isolation of MRSA or P. aeruginosa or recent hospitalization and receipt of parenteral antibiotics in the last 90 days. [75] [76]

6.1.4 Duration of Therapy

The American College of Physicians (ACP) recommends using short antibiotic treatments for CAP, with an initial duration of 5 days and reassessment of the patient's clinical improvement. [24] Similarly, the 2019 ATS/IDSA guidelines recommend at least 5 days of antibiotic therapy, but treatment should only be stopped when the patient is clinically stable, including improvement of vital signs, normal mental status, and ability to eat normally. [77]

A meta-analysis of 21 studies demonstrated that an antibiotic course of 6 days or less is as effective as a longer course while reducing mortality and serious adverse events. [6] The evidence supporting shorter-duration therapy challenges traditional 7/10 day courses and represents an important stewardship opportunity in the ED setting. [24]

Empiric antibiotic treatment should be started as soon as possible once the diagnosis of CAP has been made, according to the most likely pathogen, local microbiology, patient's risk factors for specific pathogens, pneumonia severity, patient's preference and potential antibiotic allergies, and cost-effectiveness evaluation. Guideline recommendations should be critically interpreted and individualized based on local epidemiological data and healthcare system characteristics. [76]

6.2 Urinary tract infections

Urinary tract infections are an important focus for antimicrobial stewardship in the emergency department because they are very common, are often diagnosed incorrectly, and antibiotics are frequently prescribed in an inappropriate way. This can lead to important problems, such as antimicrobial resistance and adverse drug events.

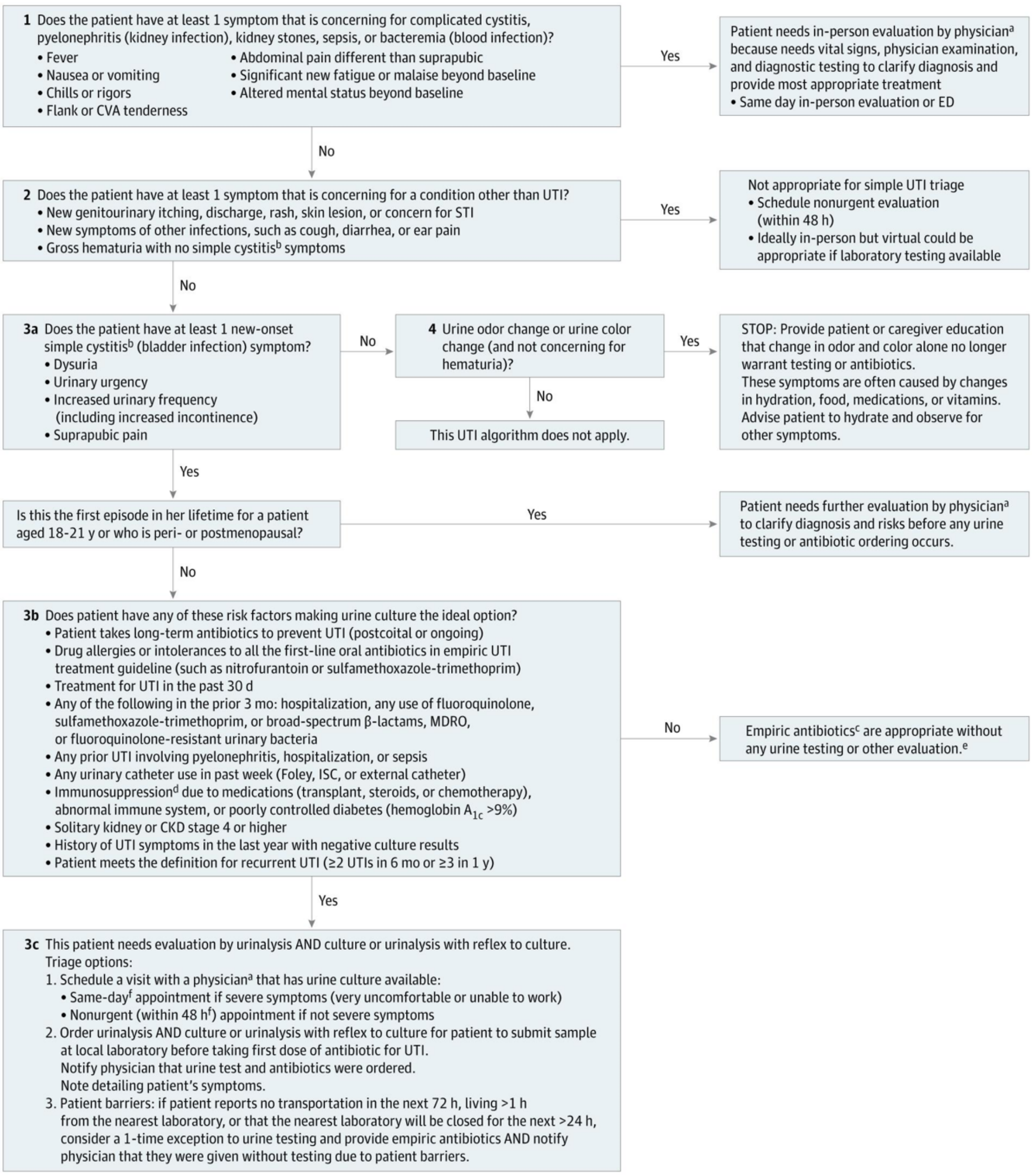
UTIs are among the most common reasons for ED visits and antibiotic prescriptions. A nationwide analysis of over 205 million ED encounters (2016–2023) found that cystitis accounted for 4.3% of all ED visits and pyelonephritis for an additional 0.5%, with both rising over time. [78]

6.2.1 Risk Stratification

The 2025 Infectious Diseases Society of America guidelines have changed the classification of UTIs, moving from a host-based definition to a symptom-based approach focused on whether the infection remains limited to the bladder or extends beyond it. [22]

- **Uncomplicated UTI (uUTI):** Infection considered confined to the bladder, with local symptoms such as dysuria, urgency, frequency, and suprapubic pain, without fever, systemic illness, flank pain, or costovertebral angle tenderness. Importantly, patients with diabetes, immunocompromised conditions, or underlying urologic abnormalities are no longer automatically classified as having a complicated UTI if symptoms remain limited to the bladder. [22]
- **Complicated UTI (cUTI):** Infection associated with symptoms suggesting spread beyond the bladder, including fever, chills, rigors, hemodynamic instability, flank pain, or costovertebral angle tenderness. Pyelonephritis is included in this category. Patients with indwelling urinary catheters, stents, or nephrostomy tubes who develop UTI symptoms are generally considered to have a complicated UTI. [22]

The Ann Arbor Guide provides a structured triage algorithm for adults with suspected UTI, applicable to both in-person and telehealth settings: [79]



Algorithm to Determine Appropriateness of Empiric Antibiotics and/or Urine Testing for Adult Nonpregnant Women With Concerns for Urinary Tract Infection (UTI)

Diagnostic Challenges

UTI overdiagnosis is a major problem in the ED. In one study, only 48% of women diagnosed with UTI in the ED had a positive urine culture, and 57% were treated without a culture being performed. [80] Another study found that only 28% of ED patients diagnosed with UTI had symptoms consistent with UTI, suggesting that overtesting is driving inappropriate treatment. [81]

Symptoms are the most important factor in diagnosing UTIs. The 2024 Infectious Diseases Society of America / American Society for Microbiology guidelines state that urine culture is usually not recommended in patients without symptoms suggestive of UTI, such as dysuria, urgency, frequency, or costovertebral angle tenderness, even if pyuria is present. [82]

Urinalysis also has important limitations. Pyuria, detected by leukocyte esterase, is highly sensitive, with rates up to 97%, but it has low specificity. Nitrites are the most specific urinalysis finding, with specificity between 94% and 98%, although they are not present in every case. When both nitrites and leukocyte esterase are negative, UTI is unlikely. Among urinalysis findings, the white blood cell count on microscopic examination showed the best diagnostic accuracy for predicting positive urine cultures. [83] [84]

Asymptomatic bacteriuria is a very common finding and becomes more common with age, affecting more than 15% of older women and up to 50% of patients living in long-term care facilities. In most cases, it should not be treated, except in pregnant women and in patients undergoing endoscopic urologic procedures. In older adults with confusion, mental status changes, or falls but without typical urinary symptoms, bacteriuria may not be related to the clinical presentation, so it is necessary to careful evaluate the situation. [85] [86]

Misdiagnosis with sexually transmitted infections is also common. One emergency department study found that 23% of women had a positive STI test, and 64% of patients with missed STIs had initially been diagnosed with UTI instead. [80]

6.2.2 Diagnostic Stewardship

Reflex urine culture algorithms performing culture only when urinalysis meets specific thresholds (e.g., >10 WBCs per low-power field) can reduce unnecessary cultures and subsequent overtreatment, though exceptions are needed for specific populations (pregnant patients, urologic abnormalities, neutropenia). [84] [82]

6.2.3 Antibiotic Choice

Uncomplicated UTI

The antibiotic choice depends on whether the UTI is complicated or non-complicated and if the patient is a man or a woman.

In Italy, fosfomycin is currently the most commonly prescribed antibiotic for UTIs, followed by ciprofloxacin, according to the REWIND study. However, this prescribing pattern does not completely reflect current European recommendations and raises important antimicrobial stewardship concerns, especially regarding the overuse of fluoroquinolones. [87]

Ciprofloxacin remains the second most prescribed antibiotic even though European guidelines do not recommend it as first-line treatment for uncomplicated cystitis. In contrast, nitrofurantoin is still underused in Italy compared with other European countries. [87]

Current European and IDSA/ ESCMID guidelines recommend nitrofurantoin 100 mg three times daily for 6 days, fosfomycin 3 g as a single dose, pivmecillinam 400 mg three times daily for 3–7 days, and trimethoprim-sulfamethoxazole one double-strength tablet twice daily for 3 days as first-line treatments for uncomplicated cystitis. [87] [88] [89]

Fluoroquinolones such as ciprofloxacin and levofloxacin are considered alternative options only and should not be used as first-line therapy because of their collateral damage and risk of adverse effects. Their use should generally be reserved for complicated UTIs or situations in which first-line agents cannot be used. [88]

Complicated UTI / Pyelonephritis

Complicated UTIs include infections associated with anatomical or functional urinary tract abnormalities, catheter-associated UTIs (CAUTIs), pyelonephritis in men, and infections occurring in immunocompromised patients.

The 2025 Infectious Diseases Society of America guidelines recommend a stepwise approach for empiric treatment of complicated UTIs. In patients without sepsis, third- or fourth-generation cephalosporins, piperacillin-tazobactam, or fluoroquinolones are preferred over carbapenems and newer broad-spectrum agents. In patients with sepsis, broader empiric antibiotic coverage is recommended and should be guided by local resistance patterns and individual patient risk factors. [22]

For uncomplicated pyelonephritis, the American College of Physicians recommends treatment with fluoroquinolones for 5–7 days or trimethoprim-sulfamethoxazole for 14 days when susceptibility is confirmed.

For outpatient management of complicated UTI, several oral empiric treatment options are available. Fluoroquinolones such as ciprofloxacin and levofloxacin are effective, but their use is increasingly limited by high resistance rates in many areas and by concerns about adverse effects. [22] [90]

TMP-SMX may also be an option when previous urine cultures suggest susceptibility, although resistance remains a major concern. Oral third-generation cephalosporins, such as cefpodoxime, are commonly used as step-down therapy when ESBL-producing organisms are not strongly suspected. Observational studies have shown that they may have similar efficacy to fluoroquinolones or TMP-SMX in patients with gram-negative bacteremia associated with complicated UTI. [22] [90]

6..2.4 Duration of Therapy

The duration of antibiotic treatment depends on the specific drug used.

For complicated UTI and pyelonephritis, the 2025 Infectious Diseases Society of America guidelines support shorter treatment courses in patients who show clinical improvement on effective therapy. Recommended durations are 5–7 days for fluoroquinolones and about 7 days for non-fluoroquinolone antibiotics. In cases of gram-negative bacteremia from a urinary source, 7 days of treatment is generally preferred over 14 days. [22]

6.3 Skin and Soft Tissue Infections

Skin and Soft Tissue Infections are also a very frequent ED findings, and are an important stewardship target.

6.3.1 Risk Stratification

The IDSA divides skin and soft tissue infections (SSTIs) into two main groups: purulent infections (such as abscesses, furuncles, and carbuncles) and nonpurulent infections (such as cellulitis, erysipelas, and necrotizing fasciitis). Each group is then classified by severity [91]:

- **Mild infections**, For purulent infections, incision and drainage (I&D) alone is usually enough. For nonpurulent infections, patients typically have cellulitis or erysipelas without systemic signs of infection, and oral antibiotics targeting streptococci are recommended.

- **Moderate infections**, Patients show systemic signs of infection, including at least one SIRS criterion such as temperature >38°C, heart rate >90 bpm, respiratory rate >24/min, or WBC >12,000 or <400. In patients with only one SIRS criterion, oral antibiotics may still be appropriate, while the presence of two or more criteria should prompt consideration of IV antibiotics. [91] [92]
- **Severe infections**, These include patients who fail initial therapy, develop hypotension, are immunocompromised, or show rapid progression of infection. These cases require IV antibiotics, MRSA coverage, and surgical evaluation to rule out necrotizing infection. [91]

The EGS grading scale (grades I–V) has also been validated in a multicenter study involving 12 centers. Higher grades (IV–V), which represent invasive or necrotizing infections, were strongly associated with higher complication rates, ICU admission, and mortality. [93]

6.3.2 Diagnostic Challenges

Pseudocellulitis, meaning conditions that look like cellulitis but are not true infections, is a major source of diagnostic mistakes. Studies show that cellulitis is misdiagnosed in up to 30% of admitted patients, and in hospitalized patients who required dermatology consultation, the misdiagnosis rate reached 74%. [92]

The most frequent mimic is stasis dermatitis. Unlike cellulitis, it is usually bilateral, while bilateral cellulitis without skin trauma is very uncommon. [92] Other common conditions that can mimic cellulitis include gout, especially when it involves a joint and causes fever or leukocytosis, as well as hematoma, contact dermatitis, deep vein thrombosis , erythema migrans, and calciphylaxis. [92] Some tools may help clinicians distinguish true cellulitis from pseudocellulitis. The ALT-70 score, which includes asymmetry, leukocytosis, tachycardia, and age ≥70 years, together with thermal imaging, has shown good diagnostic performance. When used together, these methods reached a sensitivity greater than 90% with improved specificity compared with either tool alone. [94] Differentiating cellulitis from necrotizing fasciitis is the most important diagnostic challenge. Some clinical features strongly suggest necrotizing fasciitis, including pain that is disproportionate to clinical findings, hemorrhagic bullae, skin necrosis, wooden-hard induration of the subcutaneous tissues, hypotension, and crepitus. [91] [95]

The LRINEC score, based on CRP, white blood cell count, hemoglobin, sodium, creatinine, and glucose levels, may help estimate the risk of necrotizing infection. In this study, a score ≥6 had a positive predictive value of 92%. However, a low LRINEC score does not exclude necrotizing fasciitis. When clinical suspicion remains high, close monitoring with repeated examinations every 4–6 hours and early surgical exploration are still considered the standard approach. [96]

6.3.3 Antibiotic Choice

Empiric antibiotic selection depends on whether the infection is purulent or nonpurulent and on the severity of disease.

For mild nonpurulent cellulitis or erysipelas, oral antibiotics targeting streptococci are usually sufficient, including penicillin, amoxicillin, cephalexin, dicloxacillin, or clindamycin. In moderate infections, intravenous therapy may be required, with options such as cefazolin, ceftriaxone, or penicillin G; clindamycin can be used in patients with beta-lactam allergy. Severe nonpurulent cellulitis requires broad-spectrum intravenous treatment, typically vancomycin plus piperacillin-tazobactam or a carbapenem, and surgical evaluation is often necessary. [91] [97]

For purulent skin infections such as abscesses or carbuncles, management also depends on severity. Mild infections are usually treated with incision and drainage (I&D) alone. Moderate purulent infections require I&D plus oral antibiotics active against MRSA, such as TMP-SMX, doxycycline, or clindamycin. Severe purulent infections need I&D together with intravenous MRSA-active therapy, including vancomycin, daptomycin, linezolid, or ceftaroline. [91] [97] MRSA coverage is generally not necessary for nonpurulent cellulitis unless specific risk factors are present, such as penetrating trauma, previous MRSA colonization or infection, injection drug use, or failure of initial therapy. [91] [98]

6.3.4 Duration of Therapy

The duration of therapy should be guided by the patient's clinical response rather than by a fixed treatment course.

For uncomplicated cellulitis, a 5–6 day course is generally sufficient if clinical improvement has occurred, according to ACP and IDSA recommendations. Residual erythema or inflammation at day 5 does not necessarily require prolongation of therapy because cellulitis is a paucibacillary infection and the inflammatory response may persist even after bacterial clearance. [97] [91] [92] . For purulent skin and soft tissue infections (SSTIs), when antibiotics are indicated in addition to incision and drainage, treatment is usually continued for 5–7 days. [99]

In severe or complicated SSTIs, the IDSA recommends treatment for 7–14 days, with duration individualized according to clinical response. [91] Transition from intravenous to oral antibiotics is recommended after at least 48 hours of apyrexia (temperature <37.8°C) together with regression of inflammation from the original skin markings. [92]

Patients should be reassessed after 24–48 hours. Lack of clinical improvement should prompt evaluation for resistant pathogens, alternative diagnoses such as pseudocellulitis, or deeper infections. [92]

7. STEWARDSHIP INTERVENTIONS TARGETING COMMON ED SYNDROMES

Effective antimicrobial stewardship interventions in the emergency department target common infectious syndromes through multifaceted strategies including clinical pathways, pharmacist involvement, audit and feedback, and behavioral nudges. Evidence demonstrates significant improvements in appropriate prescribing, reduced broad-spectrum antibiotic use, and preserved clinical outcomes across respiratory infections, urinary tract infections, skin and soft tissue infections, and pneumonia [21] [29] [4].

Key ED syndromes represent high-yield targets for antimicrobial stewardship because they account for a substantial proportion of antibiotic prescribing and are frequently associated with inappropriate treatment choices.

For urinary tract infections, cystitis accounts for 4.3% of all ED encounters and pyelonephritis for 0.5%, making UTIs an important area for intervention [81]. Successful strategies include treatment algorithms integrated into the electronic health record, guideline dissemination, electronic order sets, and audit and feedback. In one multifaceted intervention, adherence to the protocol increased from 41% to 84%, while fluoroquinolone use decreased from 19.1% to 5%; adherence remained high over the following 11 months with monthly text-message reminders [49]. Another effective approach is the use of nitrofurantoin as first-line therapy for uncomplicated cystitis, which was independently associated with fewer 30-day return visits, without increasing bug-drug mismatches [72]. Diagnostic stewardship is also central and is often framed through the “five Ds”: right diagnosis, drug, dose, duration, and de-escalation. Practical tools include reflex urine cultures, computerized decision support, and modified culture reporting. [103]

Respiratory infections are also a frequent source of inappropriate antibiotic prescribing. In a large urgent-care network intervention, overall antibiotic prescribing for respiratory conditions decreased from 48% to 26% during the sustainability phase. For tier 3 respiratory conditions, where antibiotics are generally not indicated, such as bronchitis, prescribing fell from 19% to 6%. At the same time, first-line antibiotic use for conditions where antibiotics may be appropriate, including sinusitis, acute otitis media, and pharyngitis, increased from 71% to 75%. [73]

For skin and soft tissue infections, stewardship in the ED should focus on institution-specific guidelines based on local antimicrobial resistance patterns and regularly updated to reflect new antibiotics and susceptibility data. Particular attention should be given to oral antibiotic selection for outpatient treatment, with the aim of ensuring an appropriate spectrum while avoiding unnecessary broad-spectrum therapy [104]. Patient-specific factors, including infection severity, comorbidities, and prior antibiotic exposure, should also guide antibiotic choice [104].

Successful antimicrobial stewardship programs in the emergency department share several common characteristics. Effective interventions are usually based on protocols adapted to local antimicrobial resistance patterns and are integrated directly into the ED workflow through electronic health records. Real-time or near-real-time feedback to clinicians is also important to improve prescribing practices. These programs typically rely on close collaboration between emergency physicians, pharmacists, and infectious disease specialists, together with structured culture review and follow-up for patients discharged from the ED. In addition, stewardship interventions are more effective when maintained over time with reinforcement strategies, such as periodic reminders or educational updates, to preserve long-term adherence. [49]

8. BACKGROUND

Inappropriate antibiotic prescribing in the community remains an important public health problem and a major cause of antimicrobial resistance. According to data from the Italian Medicines Agency (AIFA) and national surveillance systems, Italy is among the European countries with the highest antibiotic consumption, with a large proportion of prescriptions not adhering to evidence-based criteria in terms of indication, duration, or agent selection [105].

To address this issue, the National Action Plan to Combat Antimicrobial Resistance (PNCAR), introduced in 2017, promotes the implementation of antimicrobial stewardship (AMS) programs, surveillance systems, and quality indicators to improve antibiotic use in hospitals and community settings [105] [106] [33].

The emergency department is considered a particularly high-risk setting for inappropriate antibiotic prescribing. Diagnostic uncertainty, time constraints, and overcrowding often lead clinicians to initiate empirical antibiotic therapy in the absence of a confirmed bacterial infection [56] [107]. As a result, empirical antibiotic therapy may be initiated even when bacterial infection is not fully confirmed.

Recent multicenter studies reported that inappropriate prescribing in EDs ranges from 30% to 60%, depending on the patient population and study methods [51] [71].Antibiotics are prescribed in about 13–24% of ED visits, with important differences across age groups and clinical conditions [108] [109].
Adults are more likely than children to receive inappropriate prescriptions, while the most frequent indications include respiratory tract infections, urinary tract infections, and skin and soft tissue infections, many of which are of viral or non-bacterial origin [110] [111].

A key issue is that inappropriate prescribing does not only mean prescribing antibiotics when they are not indicated. It also includes failure to adhere to local or national treatment guidelines, use of broader-spectrum agents when narrower options would be sufficient, incorrect dosing, unnecessary combination therapy, and excessive treatment duration. [51] This is particularly important at ED discharge, where antimicrobial prescriptions are often less systematically reviewed than inpatient prescriptions, despite representing a relevant component of total antibiotic exposure. Current evidence suggests that discharge prescribing remains an underexplored stewardship target, especially in adult ED populations, and that available studies are heterogeneous in terms of setting, definitions of appropriateness, and outcome measures. [53]

Among ED infectious syndromes, community-acquired pneumonia (CAP), urinary tract infections (UTIs), and skin and soft tissue infections represent high-yield targets for antimicrobial stewardship because they are frequent, clinically relevant, and associated with recurring patterns of non-adherence to guidelines. [53]
In particular CAP and urinary tract infections (UTIs) have been consistently associated with substantial opportunities for optimization at discharge, including unnecessary prescriptions and excessive duration. [81] [112].
In ED CAP management common prescribing problems include inappropriate antibiotic class selection, excessive use of fluoroquinolones or cephalosporins, unnecessary broad-spectrum coverage, inadequate use of severity assessment, and prolonged treatment duration. [113] Previous studies have shown that CAP prescribing is frequently non-guideline-concordant, particularly in hospitalized cohorts, highlighting the need for better risk stratification and discharge-specific prescribing support. [114]

For uncomplicated cystitis, first-line therapy generally includes narrow-spectrum oral agents such as nitrofurantoin, Fosfomycin, pivmecillinam, or trimethoprim-sulfamethoxazole when local resistance patterns allow it. [92] [91]

Fluoroquinolones should generally be avoided as first-line therapy when other options are available, because of collateral damage, adverse effects, and resistance selection. [115] Nevertheless, ED studies continue to report frequent use of non-first-line agents, overuse of fluoroquinolones and broad-spectrum beta-lactams, treatment in the absence of true infection, and dosing or duration errors. [81] These findings underline the importance of diagnostic stewardship, including careful interpretation of urinary symptoms, urinalysis, and urine cultures, and the use of structured algorithms to distinguish uncomplicated cystitis from more complex urinary tract infections. [116]

For erysipelas and mild nonpurulent cellulitis, guideline-based treatment should primarily target streptococci, while routine MRSA coverage is not recommended unless specific risk factors are present. [94] Common stewardship problems include unnecessary MRSA coverage, excessive use of broad-spectrum regimens, and wide variability in discharge antibiotic choices. Previous studies in ED and urgent care settings have shown that adherence to cellulitis guidelines can be limited, often because of unnecessary clindamycin or trimethoprim-sulfamethoxazole use in nonpurulent infections. At the same time, this syndrome may be more amenable to standardization when local pathways clearly define severity, oral first-line options, and duration of therapy. [95]

Although several AMS interventions, such as guideline implementation, clinician education, audit and feedback, and pharmacist-led programs, have been shown to improve antibiotic prescribing quality in EDs, [36] [117] evidence remains limited and heterogeneous, especially concerning prescriptions at the time of discharge.

In particular, relatively few studies have evaluated adult ED discharge prescriptions using syndrome-specific criteria and local therapeutic guidelines. This represents an important knowledge gap, because discharge is the point at which the ED decision is translated into outpatient antibiotic exposure, with potential consequences for adverse events, reattendance, and antimicrobial resistance in the community. The discharge phase is an important but often neglected part of antimicrobial stewardship, with reported inappropriate prescribing rates higher than 50% [21]. Studies suggest that targeted AMS interventions can significantly improve optimal prescribing—defined as guideline-concordant indication, antibiotic choice, and treatment duration—with improvements of up to 36%. Similar results have been observed with peer-comparison feedback [43] and multifaceted interventions based on clinician education and audit-feedback strategies [21].

Targeted AMS strategies are urgently needed to enhance prescribing appropriateness and reduce unnecessary antibiotic exposure in this setting. The optimization of antibiotic prescribing at ED discharge is essential to safeguard patient safety, prevent adverse outcomes, and limit the dissemination of resistant pathogens in the community [51]. Optimization of antibiotic therapy at ED discharge should focus not only on reducing antibiotic use overall, but also on improving adherence to local guidelines, selecting the narrowest effective agent, avoiding unnecessary combination therapy, and ensuring appropriate treatment duration.

This study aims to identify factors associated with inappropriate oral antibiotic treatment prescribed at the time of Emergency Department discharge in adult patients, based on the therapeutic indication according to disease-specific antibiotic guidelines and a case-by-case review conducted by an experienced infectious disease physician, and to analyze the effect of inappropriate prescriptions on ED reconsultations for any reason within 30 days of hospital discharge. The study also aims to evaluate the overall patterns of antibiotic prescribing for adult patients discharged from the Emergency Department with community-acquired pneumonia (CAP), skin and soft tissue infections/abscesses (ABSSI), and urinary tract infections (UTI), and to compare patient-related risk factors between cases of appropriate and inappropriate therapy.

9. MATERIALS AND METHODS

9.1 Design, Setting and Population

This retrospective observational study was conducted from January 1 2024 to January 21 2025, in the Emergency Departments (ED) of Modena University Hospital. All adult patients discharged home with an antibiotic prescription were eligible. Exclusion criteria were hospital admission, incomplete medical records, or absence of a defined clinical diagnosis. The study was approved by the Modena University Hospital Institutional Review Board (999/18) and all data were anonymized prior to analysis.

9.2 Data collection and outcomes

Cases were identified through an electronic text-based search of the ED discharge database, using both generic and trade names of antibiotics commonly prescribed for the empirical treatment of community-acquired infections. All retrieved records were then manually reviewed with an infectious diseases specialist to confirm eligibility and to assess the clinical appropriateness of the antibiotic prescription according to the discharge diagnosis.

Extracted clinical data included patient demographics, ED unit, discharge diagnosis, prescribed antibiotic regimen, including agent, dose, and duration, and follow-up outcomes. These included 90-day attributable mortality and ED re-consultation within 30 days after discharge for the same clinical condition. The latter was considered in line with recent literature, which identifies post-discharge revisits as a practical indicator of prescribing quality and possible diagnostic uncertainty, rather than as a strict marker of treatment failure. [76]

The primary outcomes were the appropriateness of the antibiotic indication and the overall adherence to prescribing guidelines for the selected infection types: community-acquired pneumonia (CAP), cystitis, and erysipelas/cellulitis. Overall guideline adherence was defined as the correct prescription of the antimicrobial agent, dosage, and treatment duration. This approach is consistent with previous antimicrobial stewardship studies evaluating the quality of antibiotic prescribing in Emergency Department settings. [51] [43].

The secondary outcome was re-access to the ED within 30 days after discharge for the same clinical condition, consistent with recent literature identifying post-discharge revisits as a practical indicator of prescribing quality and potential diagnostic uncertainty rather than a strict marker of therapeutic failure [76]

9.3 Study definitions: Assessment of antibiotic appropriateness

Prescriptions were initially classified as appropriate or inappropriate according to the indication, based on whether the discharge diagnosis supported the need for antibiotic therapy [118]. Prescriptions were considered inappropriate when they were given for conditions likely to have a viral origin, when no clear infectious indication was present, or when antibiotics were used for non-recommended prophylaxis, in line with previous definitions of unnecessary antibiotic use and overprescribing at discharge [76].

Antibiotic appropriateness was assessed with an infectious diseases resident, under the supervision of an experienced infectious diseases consultant, using a standardized evaluation framework based on national and international guidelines, including recommendations from the Italian Society of Infectious and Tropical Diseases, IDSA, and NICE. This approach was consistent with methods previously used in antimicrobial stewardship studies conducted in the Emergency Department. [51] [43]

Subsequently, adherence to treatment recommendations was assessed using the regional antimicrobial guidelines developed by the Emilia-Romagna PNCAR working group and available through the Firstline application. These guidelines are based on current evidence and adapted to local epidemiology, with the aim of supporting appropriate empirical antibiotic selection in community settings.

For community-acquired pneumonia, cystitis, and erysipelas/cellulitis, overall guideline adherence was defined as the simultaneous appropriateness of the four main dimensions considered: indication for antibiotic therapy, antibiotic choice, dosage, and treatment duration. These three clinical conditions were selected because they are among the most common infectious diagnoses managed in the Emergency Department and account for a substantial proportion of antibiotic prescriptions in both inpatient and outpatient care. For this reason, they represent important targets for antimicrobial stewardship interventions [110] [111] [119]. When recommendations overlapped or differed, the most conservative or locally endorsed interpretation was applied to maintain consistency.

9.4 Statistical analysis

Continuous variables were summarized as medians with interquartile ranges, while categorical variables were presented as absolute counts and percentages. Comparisons between groups were performed using non-parametric tests: the Mann–Whitney test for continuous variables and the χ^2 or Fisher's exact test for categorical variables, as appropriate. Statistical significance was defined by a two-tailed p-value below 0.05.

Descriptive analyses compared demographic, clinical, and prescription-related characteristics between appropriate and inappropriate antibiotic prescriptions in the overall cohort, and among the three diagnostic subgroups—community-acquired pneumonia, cystitis, and erysipelas or cellulitis. Differences in antibiotic class, molecule, and duration of therapy were evaluated according to the underlying diagnosis.

The Wilson score interval method was used to calculate 95% CI for proportions, corrected for population size. ORs comparing factors associated with appropriate versus inappropriate prescribing were calculated using the mid-P exact conditional maximum likelihood estimate of the OR.

10. *RESULTS*

During the study period, 30,715 Emergency Department (ED) discharges were recorded, of which 13% resulted in an antibiotic prescription at discharge. A total of 3,993 antibiotic prescriptions were reviewed. Overall, 2,156 (54%) were classified as inappropriate based on predefined clinical indication criteria. Among the 1,837 (46%) prescriptions considered appropriate, 606 (33%) were issued for infections outside the predefined target syndromes (i.e., diverticulitis, gastroenteritis, COPD exacerbation, pharyngitis, sinusitis, and otitis), while 1,230 (67%) were prescribed for community-acquired pneumonia (CAP), cystitis, or mild erysipelas/cellulitis. Within this latter subgroup, cystitis was the most frequent diagnosis (n=537, 43%), followed by CAP (n=515, 42%) and erysipelas/cellulitis (n=186, 15%).

Table 1 reports baseline characteristics according to guideline adherence of antibiotic prescribing at ED discharge. Overall, 1,230 prescriptions for the three target syndromes were included in this analysis. Of these, 728 (59.2%) were classified as non-adherent to guidelines, while 502 (40.8%) were adherent.

Table 1. Characteristics of Patients Receiving Antibiotic Therapy for CAP, UTI, and ABSSSI in the Emergency Department: Overall Population and Comparison by Guideline Adherence.

Characteristics	*Overall N=1230*	*Guidelines Non-adherent therapy N=728(59,2%)*	*Guideline-adherent therapy N=502(40,8%)*	**p-*value***
Demographics				
Sex, male		376 (51.6%)	228 (45.4%)	**0,032**
Age, *Median (IQR)*		58.8±22.0(15-103)	57.6±22.2(15-101)	0,1311
Vital Parameters ***Median (IQR)***				
Systolic blood pressure (mmHg)		130 [120 - 145]	130 [120 - 150]	0.9888
Diastolic blood pressure (mmHg)		80 [70 - 80]	80 [70 - 81.5]	0.6063
HR (bpm)		85 [75 - 98]	84 [75 - 95]	0.2274
RR (breaths/min)		16 [16 - 18]	16 [16 - 17]	0.2927
SpO2 (%)		97 [95 - 98]	97 [96 - 98]	0.2296
Temperature (°C)		36.6 [36 - 37.5]	36.5 [36 - 37.4]	0.0724
Comorbidities and extrinsic risk factors ***N (%)***				
CCI		2 (0-4)	2 (0-4)	0.298
Stroke/TIA		44 (6%)	10 (2%)	**0.0005**
Diabetes		58 (8.0%)	49 (9.8%)	0.273
Chronic cardiac disease		86 (11.8%)	48 (9.6%)	0.213
Chronic pulmonary disease		38(5.2%)	27(5,4%)	0.903
Recent hospitalization		59 (8.1%)	25 (5%)	0.033
Nursing Home residence		18 (2.5%)	10 (2.0%)	0,579
Recent antibiotic therapy		100 (13.7)	56 (11.2)	0.181
Antibiotic therapy on admission		80 (11.0%)	40 (8.0%)	0.079
Baseline laboratory parameters, ***Median (IQR)***				
Leukocytes, /mm3,		4870 (9.6-9800)	6575 (11.2-10460)	**0,039**
Platelets		27000 (83500-85000)	236000 (186000-291000)	0,289
C-reactive protein (mg/dl)		3.5 [0.7 - 9.25]	2 [0.6 - 7.57]	**0.0085**
Diagnosis, ***N (%)***				
CAP		311 (42.7%)	204 (40.6%)	0.4708
Cystitis		369 (50.7%)	168 (33.5%)	<0.0001
Erysipelas/Cellulitis		52 (7.1%)	134 (26.7%)	<0.0001
ID consultation		8 (1.1%)	24 (4.8%)	**<0.0001**

** IQR: interquartile range; HR: Hearth rate; RR: Respiratory rate; TIA: Transient ischemic attack; ID: infectious diseases*

On the total prescriptions, non-adherent antibiotic prescriptions were more frequent in male patients (51.7% vs 45.4%, p=0.032). Age was similar between groups and was not associated with prescribing adherence. Recent hospitalization was more common among patients receiving non-adherent prescriptions (8.1% vs 5.0%, p=0.033), as was a history of stroke or transient ischemic attack (6.0% vs 2.0%, p=0.001). The Charlson Comorbidity Index and most other comorbidities were comparable between groups. Vital signs at Emergency Department admission were largely similar. Among laboratory parameters, only C-reactive protein was significantly higher in the non-adherent group (3.5 vs 2.0 mg/dL, p=0.008), while other variables did not differ significantly.

The distribution of infectious syndromes varied according to prescribing adherence. Cystitis was significantly more common among non-adherent prescriptions (50.7% vs 33.5%, p<0.001), whereas erysipelas/cellulitis was more frequently associated with guideline-adherent therapy (26.7% vs 7.1%, p<0.001). Community-acquired pneumonia showed comparable distribution between groups (42.7% vs 40.6%, p=0.467). Infectious diseases consultation was more frequently observed among guideline-adherent therapy prescriptions (4.8% vs 1.1%, p<0.001), suggesting an association between specialist input and guideline-concordant antibiotic use.

Table 2. Antibiotic Prescribing Patterns and Clinical Outcomes According to Guideline Adherence in Emergency Department Patients with CAP, UTI, and ABSSSI

Characteristics	*Overall N=1230*	*Guidelines Non-adherent therapy N=728(59,2%)*	*Guideline-adherent therapy N=502 (40,8%)*	p-*value*
Antibiotic prescribed at ED discharge, ***n (%)***				
Amoxicillin/clavulanate		302 (47.6%)	332 (52.4%)	**<0.001**
Cephalosporins		189 (93.6%)	13 (6.4%)	**<0,001**
Fosfomycin		62 (50.4%)	61 (49.6%)	**0,042**
Fluoroquinolones		72 (66.7%)	36 (33.3%)	0,098
Trimethoprim-sulfamethoxazole (TMP-SMX)		56 (53.9%)	48 (46.1%)	0,247
Macrolides		30 (100%)	0 (0.0%)	**<0,001**
Nitrofurantoin		6 (0.8%)	3 (0.6%)	0,745
Tetracyclines		11 (1.5%)	9(1,8%)	0,819
Combination regimens		204(28%)	118(23,5%)	0,077
Components of Guideline Adherence (Primary Outcome), ***n (%)***				
Appropriate antibiotic selection		262 (36%)	502 (100%)	<0.0001
Appropriate treatment duration		227 (31.2)	483 (96.2)	<0.0001
Appropriate dosage regimen		558(76.8%)	498 (99.2%)	<0.0001
Appropriate Combination therapy		204 (28.0)	118 (23.5)	0.077
Clinical Outcomes, ***n (%)***				
30-day ED revisit		88 (12.1%)	56 (11.2%)	0.6527
30-day all-cause mortality		38 (5.2%)	29 (5.8%)	0.672

**ED: emergency department*

Antibiotic selection at discharge differed significantly between groups ***(Table 2).*** Amoxicillin-clavulanate and Fosfomycin were more frequently associated with guideline-concordant therapy, whereas cephalosporin use was strongly associated with non-guideline-adherent prescribing. Fluoroquinolones, trimethoprim-sulfamethoxazole, nitrofurantoin, and tetracyclines showed a non-significant trend toward higher odds of non-adherent prescribing.

By definition, guideline-adherent prescriptions demonstrated substantially higher rates of appropriate antibiotic choice, treatment duration, and dosing regimen. The largest absolute difference was observed for treatment duration, which was appropriate in 96.2% of guideline-adherent prescriptions compared with 31.2% of non-adherent prescriptions. Combination therapy was slightly more frequent among non-adherent prescriptions, although this difference was not statistically significant.

No significant differences were observed in secondary outcomes ***(Table 2).*** Emergency Department reattendance rates were 12.1% in the non-adherent group and 11.2% in the guideline-adherent group (p=0.617), while mortality rates were 5.2% and 5.8%, respectively (p=0.672).

Table 3. Characteristics of Patients According to Infection Type (Community-Acquired Pneumonia, Cystitis, and Erysipelas/Cellulitis)

Characteristics	**CAP** *N=515 (41.9%).*	**Cystitis** *N=537(43,7%)*	**Erysipelas/Cellulitis** *N=186(15,1%)*	**p-value**
Demographics				
Sex, male	280(55,52%)	217(40,4%)	107(57,7%)	**<0,001**
Age, *Median (IQR)*	56.4 ± 22.1 (14.1–101.4)	59.5 ± 22.3 (0.2–103.7)	63.5 ± 19.9 (15.5–97.1)	**<0,001**
Vital Parameters ***Median (IQR)***				
Systolic blood pressure (mmHg)	130 [120 - 140]	130 [120 - 150]	135 [125 - 150]	**0.034**
Diastolic blood pressure (mmHg)	80 (70–80)	80 [70 - 82]	80 [70 - 85]	0.2032
HR (bpm)	88 [79 - 100]	80 [72 - 92]	80 [72 - 90]	**<0.001**
RR (breaths/min)	16 [16 - 18]	16 [16 - 17]	16 [16 - 16]	**<0.001**
SpO2 (%)	96 [95 - 98]	98 [97 - 98]	97 [96 - 98]	**<0.001**
Temperature (°C)	36.9 [36 - 37.7]	36.4 [36 - 37.1]	36.6[36-37.2]	**<0.001**
Comorbidities and extrinsic risk factors ***N (%)***				
CCI	1 (0–4)	2 (0–4)	2 (1–4)	**<0,001**
Stroke/TIA	19 (3.8%)	28 (5.2%)	7 (3.8%)	0,463
Diabetes	40 (7.9%)	47 (8.8%)	20 (10.8%)	0,495
Chronic cardiac disease	56 (11.1%)	54 (10.1%)	24 (12.9%)	0,556
Chronic pulmonary disease	38 (7.5%)	19 (3.5%)	8 (4.3%)	0,014
Recent hospitalization	26 (5%)	46 (8.7%)	12 (6.5%)	0,087
Nursing Home residence	11 (2.2%)	15 (2.8%)	2 (1.1%)	0,391
Recent antibiotic therapy	56 (11.1%)	84 (15.6%)	16 (8.6%)	**0,016**
Antibiotic therapy on admission	85(16,5%)	20(3,7%)	15(8,1%)	**<0,001**
Baseline laboratory parameters, ***Median (IQR)***				
Leukocytes, /mm3,	7760 (15.29–10765)	1283 (8.42–7960)	6640 (11.54–11200)	**<0,001**
Platelets	234000 (187000–296000)	232000 (189000–278000)	200000 (160000–282000)	**0,013**
C-reactive protein (mg/dl)	5 [1.2 - 10.17]	1.3 [0.5 - 6.1]	2.85 [1 - 9.3]	**<0,001**
Urinary leukocyte esterase	14 (24.6%)	389(90,68%)	2 (66.7%)	**<0,001**
Diagnostic test performed				
Urine culture	12 (2.4%)	265 (49.4%)	0 (0%)	**<0.001**
Wound culture	0 (0%)	0 (0%)	9 (4.8%)	**<0.001**
X- ray	482 (95.1%)	128 (23.8%)	54 (29%)	**<0.001**
Ultrasound	50 (9.9%)	228 (42.5%)	50 (26.9%)	**<0,001**
ID consultation	18 (3.5%)	1 (0.2%)	13 (7%)	**<0,001**

Characteristics	**CAP** *N=515 (41.9%).*	**Cystitis** *N=537(43,7%)*	**Erysipelas/Cellulitis** *N=186(15,1%)*	**p-value**
Primary Outcomes				
Overall guideline-concordant prescribing	204 (39.5%)	168 (31.3%)	134 (72.0%)	**<0.001**
Components of Guideline Adherence (Primary Outcome), ***n (%)***				
Appropriate antibiotic choice	380 (75.0%)	222 (41.3%)	1 162 (87.1%)	**<0.001**
Appropriate treatment duration	283 (55.8%)	283 (52.7%)	144 (77.4%)	**<0.001**
Appropriate dosage regimen	455 (89.7%)	440 (81.9%)	161 (86.6%)	**<0.001**
Appropriate Combination therapy	268 (87.9%)	1 (9.1%)	0 (0.0%)	**<0,001**
Combination therapy	307 (60.5%)	11 (2.0%)	4 (2.1%)	**<0,001**
Treatment duration, Median (IQR)	7 (5–7)	5 (4–7)	7 (6–7)	**<0.001**
Clinical Outcomes				
30-day all-cause mortality	24 (4,7%)	35 (6.5%)	8 (4.3%)	0.338
ED revisit	50 (9,9%)	71 (13,2%)	23 (12.4%)	0.23

Patients were stratified into three diagnostic groups: community-acquired pneumonia (CAP), cystitis, and erysipelas/cellulitis, in order to assess differences in clinical presentation, diagnostic work-up, and antibiotic management ***(Table 3 and Supplementary Materials).***

Overall, the three syndromes showed distinct epidemiological and clinical profiles. Male sex predominated in CAP and erysipelas/cellulitis, while cystitis was more frequent in females ($p<0.001$). Patients with erysipelas/cellulitis were older compared with the other groups ($p<0.001$). Vital signs differed significantly across syndromes, with CAP showing a more severe systemic presentation (higher heart rate, respiratory rate, temperature, and lower oxygen saturation), while cystitis was associated with a milder clinical picture.

Comorbidity burden also varied, with differences in Charlson Comorbidity Index and a higher prevalence of chronic pulmonary disease in CAP ($p=0.014$). Recent antibiotic exposure was more common in cystitis ($p=0.016$). Diagnostic evaluation was syndrome-specific: CAP was characterized by near-universal chest radiography and higher inflammatory markers, cystitis by frequent urinary dipstick positivity and urine culture collection, and erysipelas/cellulitis by occasional wound cultures. Infectious diseases consultation was more frequent in erysipelas/cellulitis.

Antibiotic prescribing patterns differed substantially across syndromes. Guideline-concordant therapy was highest in erysipelas/cellulitis (72.0%), followed by CAP (39.5%) and cystitis (31.3%), mainly driven by differences in antibiotic selection and treatment duration. CAP showed a higher use of combination therapy, while cystitis was associated with the lowest adherence in antibiotic choice. Treatment duration also varied significantly, being shortest in cystitis and longer in CAP and erysipelas/cellulitis ($p<0.001$) ***(Table 3 and Figure 1).***

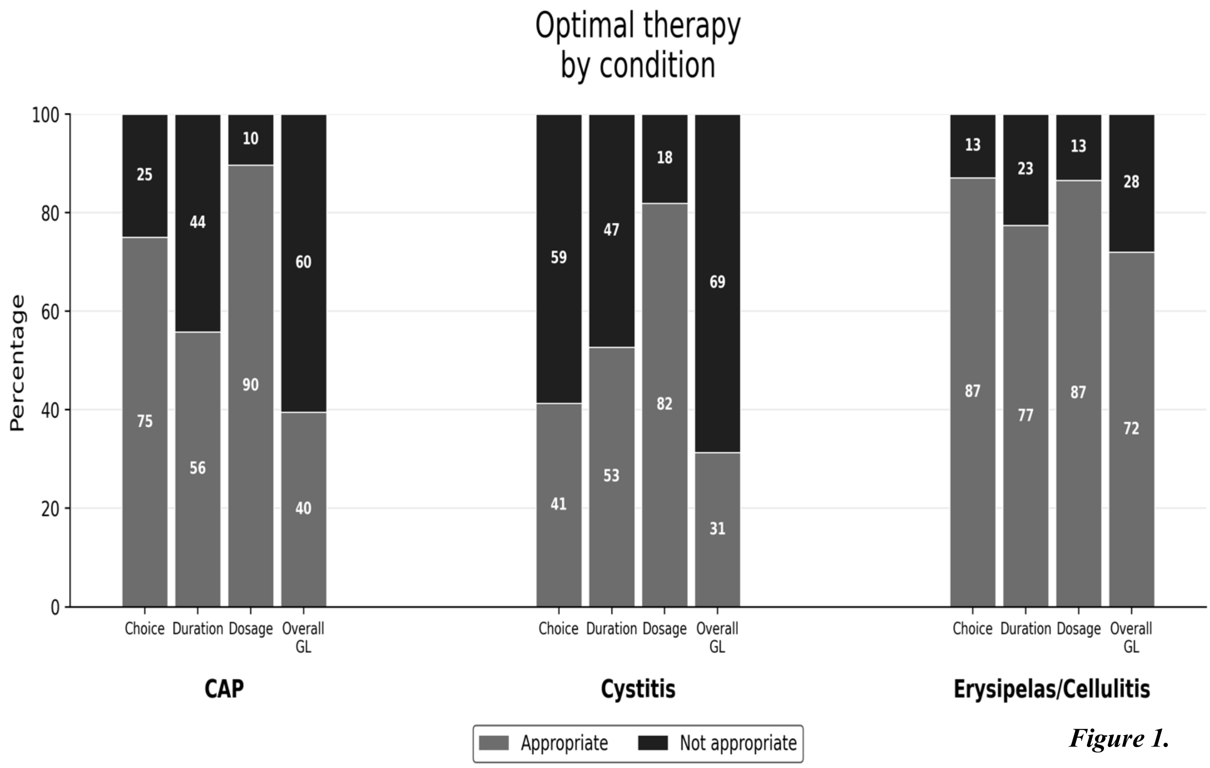


Figure 1.

Figure 1. Guideline-Concordant Antibiotic Prescribing at Discharge for Community-Acquired Pneumonia, Urinary Tract Infection, and Skin and Soft Tissue Infections, Stratified by Infection Type, with Component-Level Appropriateness of Antibiotic Choice, Treatment Duration, and Dosage Regimen.

The Figure 1 summarizes antibiotic appropriateness across conditions, including antibiotic selection, treatment duration, dosing regimen, and overall guideline concordance. Erysipelas/cellulitis demonstrated the highest rate of overall guideline-concordant prescribing, whereas cystitis showed the lowest adherence, primarily driven by incorrect first-line antibiotic molecule selection. Across all conditions, dosing regimens were more frequently appropriate than either antibiotic choice or treatment duration.

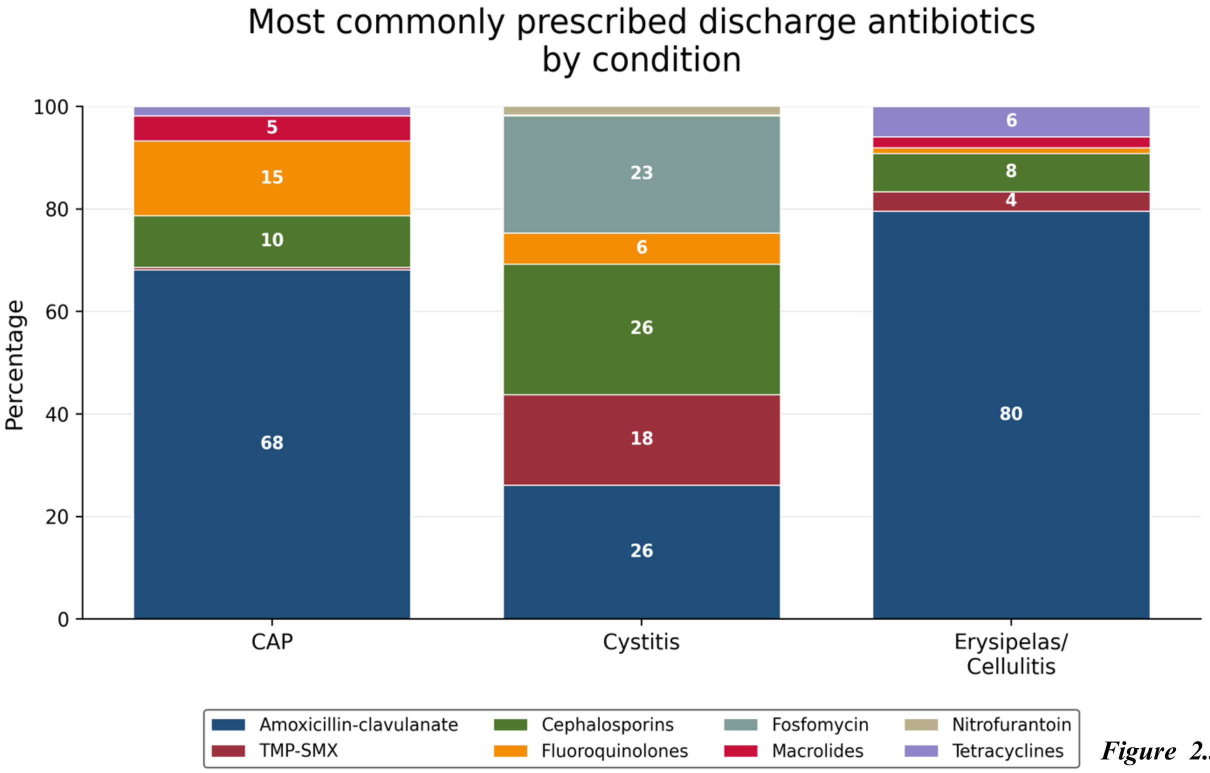


Figure 2..

Figure 2. Most Frequently Prescribed Antibiotics at Emergency Department Discharge for Community-Acquired Pneumonia, Urinary Tract Infection, and Skin and Soft Tissue Infections (N = 1,230 Encounters). **Percentages based on total number of antibiotic prescriptions.*

The Figure 2 depicts the distribution of discharge antibiotic prescriptions stratified by infectious diagnosis. Amoxicillin-clavulanate was the most frequently prescribed agent in both community-acquired pneumonia (CAP) and *erysipelas/cellulitis. In contrast, prescribing patterns for cystitis were more heterogeneous, with a broader spectrum of agents including cephalosporins, fosfomycin, amoxicillin-clavulanate, and trimethoprim-sulfamethoxazole. Cephalosporin use was particularly prominent in cystitis, while fluoroquinolone prescriptions were proportionally more frequent in CAP compared with the other diagnostic categories.*

No significant differences were observed in Emergency Department reattendance or mortality across the three groups, indicating that observed variability primarily reflected differences in clinical presentation, diagnostic approach, and prescribing quality rather than short-term outcomes.

Table 4 summarizes the multivariable logistic regression analyse performed to identify independent predictors of guideline-discordant antibiotic prescribing.

Table 4. Independent Predictors of Guideline-Discordant Antibiotic Prescribing: Multivariable Logistic Regression Analysis

	Adjusted Odds Ratio (aOR) (95% CI)	***p- value***
Male sex	1,492(1,1-198)	**0,006**
Community-acquired pneumonia (CAP)	0,609(0,41-0,89)	**0,011**
Erysipelas/Cellulitis	0,25(0,15-0,40)	**<0,001**
C-reactive protein (CRP), mg/dL	1,02(1-1,052)	**0,018**
Amoxicillin-clavulanate prescription	0,609(0,42-0,86)	**0,006**
Cephalosporin prescription	7,4(3,8-14,1)	**<0,001**
Combination antibiotic therapy	1,6(1,06-2,48)	**0,026**

In the multivariable logistic regression analysis, male sex (aOR 1.49, 95% CI 1.12–1.98; p=0.006), higher CRP levels (aOR 1.02 per mg/dL increase, 95% CI 1.00–1.05; p=0.018), cephalosporin prescribing (aOR 7.40, 95% CI 3.88–14.11; p<0.001), and combination antibiotic therapy (aOR 1.62, 95% CI 1.06–2.48; p=0.026) were independently associated with higher odds of guideline-discordant prescribing. Conversely, a diagnosis of CAP (aOR 0.61, 95% CI 0.41–0.89; p=0.011), erysipelas/cellulitis (aOR 0.25, 95% CI 0.15–0.40; p<0.001), and amoxicillin-clavulanate prescribing (aOR 0.61, 95% CI 0.42–0.86; p=0.006) were independently associated with lower odds of inappropriate antibiotic prescribing.

Table 5 compares the characteristics of patients with and without Emergency Department (ED) reattendance. Overall, 144 patients (11,7%) experienced at least one ED reattendance during follow-up, whereas 1,086 patients (88,3%) did not.

Table 5. Baseline Characteristics, Diagnostic Evaluation, Antibiotic Prescribing Patterns, and Clinical Outcomes According to 30-Day ED Reattendance

Characteristics	**No ED Reattendance** *N=1086(88,3%)*	**ED-Reattendance** *N=144(11,7%)*	**p- value**
Demographics			
Sex, male	537 (49.5)	67 (46.5)	0,51
Age, *Median (IQR)*	58.7 ± 21.9 (0.2-103.7)	59.4 ± 22.6 (14.3-96.8)	0,715
Vital Parameters *Median (IQR)*			
Systolic blood pressure (mmHg)	130 (120-145)	136.5 (120-150)	0,674
Diastolic blood pressure (mmHg)	80 (70-80)	80 (70-85)	0,746
HR (bpm)	85 (75-98)	80 (74.5-93.5)	0,075
RR (breaths/min)	16 (16-17)	16 (16-17)	0,97
SpO2 (%)	97 (95-98)	98 (96-98)	0,476
Temperature (°C)	36.6 (36-37.5)	36.5 (36-37.3)	0,16
Comorbidities and extrinsic risk factors N(%)			
CCI	2 (0-4)	2 (0-4.5)	0,092
Solid cancer	68 (6.3%)	15 (10.4%)	**0,062**
Chronic cardiac disease	55 (5.1)	10 (6.9)	0,343
Chronic pulmonary disease	30 (2.8)	6 (4.2)	0,348
Recent hospitalization	76 (7.0%)	8 (5.6%)	0,519
Nursing Home residence	25 (2.3%)	3(2,1%)	0,869
Recent antibiotic therapy	135 (12.4%)	21 (14.6%)	0,466
Antibiotic therapy on admission	108 (9.9)	12 (8.3)	0,540
Baseline Laboratory parameters, Median (IQR)			
Leukocytes, /mm3,	6275 (10.3-10180)	1480 (892-8150)	**0,002**
Platelets	231000 (184000-288000)	231000 (186000-290000)	0,642
C-reactive protein (mg/dl)	2.8 (0.62-8.7)	2.5 (0.7-9.2)	0,826
Creatinine	0.88 (0.72-1.07)	0.89 (0.72-1.1)	0,681
Diagnostic test			
Urine culture	227 (20.9%)	50 (34.7%)	**<0,001**
Ultrasound	277 (25.5%)	51 (35.4%)	0,641
X- ray	590 (54.3%)	74 (51.4%)	0,012
ID consultation	26 (2.4%)	6 (4.2%)	0,209
Diagnosis, ***N (%)***			
CAP	463 (42.6%)	52 (36.1%)	0,136
Cystitis	466 (42.9%)	71 (49.3%)	0,146
Erysipelas/Cellulitis	163 (15.0%)	23 (16.0%)	0,762
Primary Outcomes			

Overall guideline-concordant prescribing	446(41,07%)	56(38,89%)	0,617
Components of Guideline Adherence (Primary Outcome), n(%)			
Appropriate antibiotic choice	685 (63.1%)	79 (54.9%)	0,056
Appropriate treatment duration	616 (56.7%)	94 (65.3%)	**0,051**
Appropriate dosage regimen	926 (85.3%)	130 (90.3%)	0,105
Appropriate Combination therapy	251 (86.2%)	18 (62.1%)	**<0,001**
Combination therapy	293 (27.0%)	29 (20.1%)	0,079
Treatment duration, Median (IQR)	6 (5-7)	7 (5-7)	0,265
Clinical Outcomes			
Death	55 (5.1%)	12 (8.3%)	0,104

Baseline characteristics were largely comparable between patients with and without ED reattendance. No significant differences were observed in sex, age, recent hospitalization, nursing home residence, Charlson Comorbidity Index, underlying comorbidities, or vital signs at ED presentation. The only exception was the presence of solid malignancy, which was significantly more frequent among patients who were subsequently readmitted to the ED.

Similarly, inflammatory and renal laboratory parameters, including C-reactive protein (CRP), platelet count, and serum creatinine levels, were comparable between groups. However, patients who reattended the ED had a significantly lower white blood cell count at the index visit.

Urine cultures were performed more frequently in patients who subsequently reattended the ED compared with those who did not (34.7% vs. 20.9%, $p < 0.001$). In contrast, the distribution of infectious syndromes did not differ significantly between the two groups.

Table 6. Predictors of Emergency Department readmission: univariate and multivariate logistic regression analysis.

ED readmission	***Adjusted Odds Ratio (aOR) (95% CI)***	***p- value***
Solid Cancer	1,8(0,99-3,26)	0,052
Amoxicillin-clavulanate prescription	0,7(0,48-1,08)	0,120
Cephalosporin prescription	1,65(1,03-2,64)	0,035
Inappropriate treatment duration	1,53(1,06-2,22)	0,022

In the multivariable analysis of predictors of ED readmission, solid cancer showed a borderline association with increased risk of readmission (aOR 1.8, 95% CI 0.99–3.26; p=0.052).

Among antibiotic-related variables, cephalosporin use was independently associated with higher odds of ED readmission (aOR 1.65, 95% CI 1.03–2.64; p=0.035), while amoxicillin-clavulanate showed a non-significant trend toward a protective effect (aOR 0.7, 95% CI 0.48–1.08; p=0.120).

Inappropriate treatment duration was independently associated with increased odds of ED readmission (aOR 1.53, 95% CI 1.06–2.22; p=0.022). In contrast, no independent association was observed for combination therapy or appropriate antibiotic choice after adjustment.

Supplementary data.

Table S1 presents the subgroup analysis of patients discharged from the Emergency Department with a diagnosis of community-acquired pneumonia. Overall, 515 patients with CAP were included; 311 prescriptions (60.4%) were classified as inappropriate and 204 (39.6%) as appropriate according to local guidelines.

Table S1. Baseline Characteristics, Diagnostic Work-up, Prescribing Patterns, and Outcomes of Patients with Community-Acquired Pneumonia According to Prescribing Appropriateness.

ALL CAP N=515			
	Inappropriate prescribing	**Overall guideline-concordant prescribing**	**p- value**
Demographics			
Sex, male	170(54,66%)	116(56,86%)	0,623
Age, Median (IQR)	55.9 ± 22.3 (14.1–101.4)	57.6 ± 21.8 (14.2–98.7)	0,388
Vital Signs			
Systolic blood pressure (mmHg)	130 (120–140)	130 (120–145)	0,512
Diastolic blood pressure (mmHg)	79 (70–80)	76 (70–80)	0,821
HR (bpm)	88 (78–101)	88 (80–100)	0,697
RR (breaths/min)	16 (16–18)	16 (16–18)	0,195
SpO2 (%)	96 (95–98)	96 (95–98)	0,139
Temperature (°C)	36.9(36.2-37.7)	36.9 (36.–37.8)	0,516
CURB-65	0 (0–1)	0 (0–1)	0,82
Comorbidities			
CCI	1 (0–4)	2 (0–4)	0,587
Chronic Cardiac disease	39(12,54%)	21(10,29%)	0,437

Chronic pulmonary disease	20(6,43%)	20(9,80%)	0,162
Other Risk factors			
Recent antibiotic therapy	30 (9.7%)	28 (13.7%)	0,152
Antibiotic therapy on admission	56 (18.0%)	29 (14.2%)	0,257
Recent hospitalization	17(5,47%)	9(4,41%)	0,593
Nursing Home residence	8(2,57%)	3(1,47%)	0,398
Laboratory and diagnostic investigations			
CRP (mg/dl)	5.5 (1.4–10.6)	3.5 (1.1–9.8)	0,079
White blood cell count	7410 (11.99–10180)	8120 (4640–10930)	0,087
X- ray	293 (94.2%)	197 (96.6%)	0,224
Infectious disease consultation	5 (1.6%)	13 (6.4%)	**0,004**
Antibiotic type prescribed at dishcarge			
Penicillins(Amoxicillin-clavulanate)	192 (61.7%)	156 (76.5%)	<0.001
Cephalosporins	47 (15.1%)	6 (2.9%)	<0,001
Fluoroquinolones	41 (13.2%)	35 (17.2%)	0,214
Macrolides	25 (8.0%)	0 (0.0%)	<0,001
Caracteristics of discharge prescription			
Combination therapy	196 (63.0%)	115 (56.4%)	0,131
Correct combination therapy	159 (81.5%)	110 (96.5%)	<0,001
Appropriate antibiotic choice	184 (59.2%)	204 (100.0%)	<0,001
Appropriate treatment duration	95 (30.6%)	194 (95.1%)	<0,001
Appropriate dosage regimen	260 (83.6%)	203 (99.5%)	<0,001
Death	17 (5.5%)	9 (4.4%)	0,593
ED revisit	37 (11.9%)	15 (7.3%)	0,094

Among patients discharged with community-acquired pneumonia, those receiving inappropriate prescriptions and those receiving guideline-concordant therapy were broadly comparable in terms of demographics, vital signs, comorbidities, CURB-65 score, and inflammatory markers. Guideline-concordant prescribing was associated with more frequent infectious disease consultation and greater use of amoxicillin-clavulanate, whereas cephalosporins and macrolides were more frequent among inappropriate prescriptions. No significant differences were observed in mortality or ED revisit rates.

Table S2 reports the subgroup analysis of patients discharged with a diagnosis of cystitis. Overall, 537 patients were included; 369 prescriptions (68.7%) were classified as inappropriate and 168 (31.3%) as appropriate according GL.

Table S2. Baseline Characteristics, Diagnostic Work-up, Prescribing Patterns, and Outcomes of Patients with Cystitis According to Prescribing Appropriateness.

ALL Cystitis N=537	**Inappropriate prescribing**	**Overall guideline-concordant prescribing**	**p- value**
Demographics			
Sex, male	176 (47.7%)	41 (24.4%)	<0.001
Age, Median (IQR)	62.4 ± 21.2 (0.2–103.7)	53.1 ± 23.5 (14.7–101.6)	<0.001
Vital Signs			
HR (bpm)	82 (73–95)	80 (70–90)	0,077
SpO2 (%)	98 (96–98)	98 (97–99)	0,015
Temperature (°C)	36.5 (36–37.3)	36.3 (36–37)	0,087
Comorbidities			
CCI	2 (0–4)	1 (0–3)	**0,001**
Diabetes	33 (8.9%)	14 (8.3%)	0,817
Chronic Cardiac disease	40 (10.8%)	14 (8.3%)	0,37

Stroke/TIA	27 (7.3%)	1 (0.6%)	**0,001**
Chronic kidney disease	13 (3.5%)	6 (3.6%)	0,978
Others risk factors			
Recent antibiotic therapy	63 (17.1%)	21 (12.5%)	0,176
Antibiotic therapy on admission	15 (4.1)	5 (3.0)	0,603
Recent hospitalization	39 (10.6%)	7 (4.2%)	**0,014**
Colonization	6 (1.6%)	1 (0.6%)	0,329
Laboratory and diagnostic investigations			
CRP (mg/dl)	1.6 (0.5–7.7)	0.85 (0.5–3.1)	**<0,001**
White blood cell count	12.47 (8.26–8330)	13.31 (8.8–7510)	0,669
Neutrophils %	73.95 (63.9–82)	71.1 (60.7–79.3)	0,066
Creatinine	0.9 (0.73–1.11)	0.8 (0.69–0.97)	**0,001**
Platelets	229000(180000–275000)	240000 (207000–290000)	0,008
Ultrasound	165 (44.7%)	63 (37.5%)	0,117
Infectious disease consultation	0 (0.0%)	1 (0.6%)	0,138
Antibiotic type prescribed at dishcharge			
Penicillins(Amoxicillin-Clavulanate)	84 (22.8%)	56 (33.3%)	0,010
Fosfomycin	62 (16.8%)	61 (36.3%)	**<0,001**
Bactrim	55 (14.9%)	40 (23.8%)	0,012
Cefalosporins	132 (35.8%)	5 (3.0%)	**<0,001**
Fluoroquinolones	29 (7.9%)	3 (1.8%)	0,005
Characteristics of discharge prescription			
Appropriate antibiotic choice	54 (14.6%)	168 (100.0%)	<0,001
Appropriate treatment duration	122 (33.1%)	161 (95.8%)	<0,001

Appropriate dosage regimen	272 (73.7%)	168 (100.0%)	<0,001
Death	21 (5.7%)	14 (8.3%)	0,25
ED revisit	47 (12.7%)	24 (14.3%)	0,623

In the cystitis subgroup, inappropriate prescribing was more frequent among older patients, males, and those with higher comorbidity burden, previous stroke/TIA, recent hospitalization, higher CRP, and higher creatinine levels. Inappropriate prescriptions were strongly associated with cephalosporin and fluoroquinolone use, whereas guideline-concordant therapy more often included fosfomycin, trimethoprim-sulfamethoxazole, and amoxicillin-clavulanate. Despite marked differences in prescribing appropriateness, mortality and ED revisit rates did not differ significantly between groups.

Table S3 reports the subgroup analysis of patients discharged with a diagnosis of erysipelas/cellulitis. Overall, 186 patients were included; 52 prescriptions (28.0%) were classified as inappropriate and 134 (72.0%) as appropriate, confirming that this syndrome had the highest rate of guideline-concordant prescribing.

Table S3. Baseline Characteristics, Diagnostic Work-up, Prescribing Patterns, and Outcomes of Patients with Cellulitis/Erysipelas According to Prescribing Appropriateness.

ALL Cellulitis/Erysipelas N=186	**Inappropriate prescribing**	**Overall guideline-concordant prescribing**	**p- value**
Demographics			
Sex, male	32 (61.5%)	75 (56.0%)	0,491
Age, Median (IQR)	63.5 ± 20.3 (20.5–97.1)	63.5 ± 19.8 (18.9–92)	0,989
Vital Signs			
HR (bpm)	80 (72–88)	80 (71–92)	0,733

Temperature (°C)	36.8 (36–37.3)	36.5 (36–37.2)	0,266
Comorbidities			
CCI	2 (1–4.5)	3 (0–4)	0,869
Diabetes	4 (7.7%)	16 (11.9%)	0,401
Chronic Cardiac disease	9 (17.3%)	15 (11.2%)	0,264
Chronic kidney disease	2 (3.9%)	6 (4.5%)	0,849
Others risk factors			
Recent antibiotic therapy	7 (13.5%)	9 (6.7%)	0,141
Antibiotic therapy on admission	9 (17.3%)	6 (4.5%)	0,004
Recent hospitalization	3 (5.8%)	9 (6.7%)	0,813
Laboratory and diagnostic investigations			
CRP (mg/dl)	3.05 (1.1–8.7)	2.45 (0.8–9.55)	0,353
White blood cell count	8770 (3880–10960)	6050 (10.63–11300)	0,154
ALT	20.5 (14–31)	16.5 (12–23)	0,044
Creatinine	0.93 (0.78–1.12)	0.98 (0.82–1.14)	0,297
Wound Culture	1 (1.9%)	8 (6.0%)	0,248
Ultrasound	11 (21.1%)	39 (29.1%)	0,272
Infectious disease consultation	3 (5.8%)	10 (7.5%)	0,684
Antibiotic type prescribed at dishcharge			
Penicillins(Amoxicillin-Clavulanate)	26 (50.0%)	122 (91.0%)	<0,001
Cephalosporins	12 (23.1%)	2 (1.5%)	<0,001
Tetracyclins	8 (15.4%)	3 (2.2%)	0,001
Macrolides	4 (7.7%)	0 (0.0%)	0,06
Fluoroquinolones	2 (3.9%)	0(0,0%)	0,077
Characteristics of discharge prescription			

Appropriate antibiotic choice	28 (53.9%)	134 (100.0%)	<0,001
Appropriate treatment duration	12 (23.1%)	132 (98.5%)	<0,001
Appropriate dosage regimen	30 (57.7%)	131 (97.8%)	<0,001
Death	0 (0.0%)	8 (6.0%)	0,072
ED revisit	6 (11.5%)	17 (12.7%)	0,831

Among patients with erysipelas/cellulitis, guideline-concordant prescribing was more frequent than inappropriate prescribing, confirming this diagnosis as the subgroup with the highest adherence rate. Baseline demographic, clinical, comorbidity, laboratory, and diagnostic characteristics were largely similar between the two groups. However, antibiotic therapy at admission was significantly more frequent among patients with inappropriate prescriptions, and ALT values were slightly higher in this group. Guideline-concordant therapy was strongly associated with amoxicillin-clavulanate use, whereas cephalosporins and tetracyclines were more frequently prescribed in the inappropriate group. The main differences concerned prescribing quality, with guideline-concordant cases showing substantially higher rates of appropriate antibiotic choice, treatment duration, and dosage regimen. Mortality and ED revisit rates did not differ significantly between groups.

The following tables report the univariate and multivariate logistic regression analyses performed to identify factors associated with inappropriate antibiotic prescribing within all patients, each infectious syndrome and also with ED readmission in the overall cohort. For the diagnosis-specific models, the outcome was inappropriate prescribing, defined as non-guideline-concordant therapy. Therefore, odds ratios above 1 indicate an increased likelihood of inappropriate prescribing, whereas odds ratios below 1 indicate a reduced likelihood of inappropriate prescribing.

Table S4. Predictors of inappropriate antibiotic prescribing in community-acquired pneumonia: univariate and multivariate logistic regression analysis.

CAP	Univariate OR (IC 95%)	p-value	Multivariate aOR (IC 95%)	p-value
Infectious disease consultation	0,240 (0,084–0,684)	0,008	0,23(0,08-0,69)	0,009
Penicillins(Amoxicillin-clavulanate)	0,496 (0,334–0,738)	0,001	0,39(0,22-0,69)	0,001
Cephalosporins	5,875 (2,463–14,015)	<0,001	2,7(1,03-7,22)	0,043
				0,004
Association therapy	1,319 (0,920–1,891)	0,132	2(1,24-3,22)	0,002

In patients with community-acquired pneumonia, infectious disease consultation and amoxicillin-clavulanate prescription were independently associated with lower odds of inappropriate prescribing. Conversely, cephalosporin use and combination therapy were associated with increased adjusted odds of non-guideline-concordant treatment. These findings suggest that, in CAP, inappropriate prescribing was mainly driven by antibiotic class selection and the use of association therapy, whereas specialist consultation has been demonstrated to be having a protective role.

Table S5. Predictors of inappropriate antibiotic prescribing in cystitis: univariate and multivariate logistic regression analysis.

Cystitis	Univariate OR (IC 95%)	p-value	Multivariate aOR (IC 95%)	p-value
Sex,male	2,825 (1,880–4,244)	<0,001	2,2(1,35-3,58)	0,001
Recent hospitalization	2,718 (1,190–6.211)	0,018	2,26(0,88-5,7)	0,089
Stroke/TIA	13,184 (1,776–97,856)	0,012	4,99(0,61-40,89)	0,134
Platelets	1,000 (0,019–1.000)	0,019	0,99(0,99-0,99)	0,016
Cephalosporins	18,157 (7,272–45,332)	<0,001	15,55(6,07-39,83)	<0,001
Fluoroquinolones	4,691 (1,409–15,624)	0,012	5,44(1,56-18,9)	0,008

In the cystitis subgroup, male sex, cephalosporin use, and fluoroquinolone prescription remained independently associated with inappropriate prescribing after multivariate adjustment. Recent hospitalization and previous stroke/TIA were significant only in the univariate analysis, suggesting that their effect was partly explained by other covariates. Cephalosporins represented the strongest predictor of inappropriate therapy, highlighting cystitis as a key target for antimicrobial stewardship interventions.

Table S6. Predictors of inappropriate antibiotic prescribing in Erysipelas/cellulitis: univariate and multivariate logistic regression analysis.

Erisypela/Cellulitis	Univariate OR (IC 95%)	p-value	Multivariate aOR (IC 95%)	p-value
Sex,male	1.259 (0.654–2.422)	0,491	2.54(0.69- 9.2)	0,159
GCS	1,036 (0,749–1,434)	0,831	0,14(0,02-1,06)	0,058
ALT	1,012 (0,989–1,036)	0,304	1,02(0,99-1,05)	0,111
Penicillins(Amoxicillin-clavulanate)	0,098 (0,044–0,220)	<0,001	0,118(0,03-0,454)	0,002
Cephalosporins	19,800 (4,252–92,191)	<0,001	5,5(0,44-68,36)	0,184

Among patients with erysipelas/cellulitis, amoxicillin-clavulanate was the only variable independently associated with lower odds of inappropriate prescribing. Although cephalosporins showed a strong association with inappropriate therapy in the univariate analysis, this association was no longer significant after adjustment, probably reflecting limited sample size and wide confidence intervals. Overall, these results confirm that guideline adherence in erysipelas/cellulitis was mainly related to the use of recommended first-line therapy.

11. DISCUSSION

Main results

This study shows that antibiotic prescribing at Emergency Department (ED) discharge remains a major antimicrobial stewardship issue. Among 30,715 ED discharges, 13% resulted in an antibiotic prescription. Overall, more than half of the reviewed antibiotic prescriptions were classified as inappropriate according to predefined clinical criteria. When the analysis was restricted to the three target syndromes, community-acquired pneumonia (CAP), cystitis, and mild erysipelas/cellulitis, 728 of 1,230 prescriptions (59.2%) were non-guideline-concordant, whereas only 502 (40.8%) were fully adherent to local recommendations. These findings indicate that antibiotic prescribing at ED discharge represents a relevant and measurable target for antimicrobial stewardship interventions in this setting.

The burden of inappropriate prescribing observed in this study is consistent with the literature on antibiotic overuse during transitions of care. Vaughn et al. showed that antibiotic overuse after discharge occurred in 49.1% of 21,825 adult patients treated for pneumonia or urinary tract infection across 46 hospitals, with wide between-hospital variation and condition-specific drivers of overuse [120]. Similarly, the ROAD Home framework identified discharge as a particularly vulnerable point for antibiotic overuse and emphasized unnecessary therapy, excessive duration, avoidable fluoroquinolone use, and inappropriate intravenous therapy as key targets for stewardship interventions [53]. Our study extends these observations to the adult ED discharge setting, where decisions are made under time pressure and often without microbiological confirmation, and demonstrates that the same transition-of-care problem also affects oral antibiotic prescriptions issued directly from the ED.

The pattern of non-adherence was strongly syndrome-specific. Cystitis was the most frequent diagnosis in the target cohort and had the lowest rate of guideline-concordant therapy (31.3%). CAP showed intermediate adherence (39.5-39.6%), while erysipelas/cellulitis had the highest adherence (72.0%). This heterogeneity is important because it suggests that inappropriate discharge prescribing is not a single uniform behavior. Rather, it reflects different diagnostic and therapeutic challenges across syndromes. Therefore, ED stewardship interventions should be syndrome-specific rather than based only on global restriction of antibiotic use.

Cystitis emerged as the main area for improvement. This finding is aligned with previous studies showing that suspected urinary tract infections are frequently overdiagnosed and overtreated in ED settings. Chardavoyne and Kasmire found that culture-confirmed infection was present in only 47% of adults diagnosed with cystitis who underwent urine culture, and that appropriate antibiotic selection was achieved in 68% of adults with cystitis; even when the antibiotic type was appropriate, dosing and duration errors occurred in 44% of prescriptions [121]. In this study, in the cystitis subgroup, inappropriate prescribing was independently associated with male sex, cephalosporin use, and fluoroquinolone use. This pattern reflects a major stewardship problem: the use of broader-spectrum agents when first-line oral options would usually be preferred. Current evidence and guidelines support narrow-spectrum agents such as Fosfomycin, nitrofurantoin, pivmecillinam, or trimethoprim-sulfamethoxazole as first-line options for uncomplicated cystitis, while fluoroquinolones should generally be avoided as first-line therapy because of collateral damage and adverse-effect concerns [90] [91]. Similar concerns have been reported in ED-based studies of UTI prescribing, where inappropriate antibiotic choice, treatment in the absence of true infection, and dosing or duration errors were common [120].

The CAP findings also align with previous literature, although the degree of inappropriateness observed in our cohort was lower than that reported in some hospitalized adult populations. Lawless et al. found that antimicrobial prescribing for CAP was inappropriate in 80% of adult hospitalized patients, with frequent misuse of ceftriaxone, limited documented use of pneumonia severity scores, and no observed difference in mortality according to prescribing appropriateness [122]. In the present study, 311 of 515 CAP prescriptions were inappropriate (60.4%). In this subgroup, prescribing gaps involved both treatment-duration errors and antibiotic-selection issues, particularly cephalosporin use and combination therapy. Moreover, infectious disease consultation and amoxicillin-clavulanate use were associated with lower odds of inappropriate prescribing. These findings are consistent with CAP guideline principles, which emphasize risk stratification, antibiotic selection according to disease severity and patient characteristics, and short courses of therapy once clinical stability has been achieved [77] [78] [80].

Treatment duration emerged as a key component of prescribing quality. In the overall target population, appropriate antibiotic choice was achieved in 62.1% of prescriptions, whereas duration adherence was lower, at 57.7%. Among non-guideline-concordant prescriptions, duration was appropriate in only 31.2%, compared with 96.2% among guideline-concordant prescriptions. These findings suggest that duration was not a secondary technical issue, but one of the main drivers of overall inappropriateness. A similar pattern has been reported in pediatric discharge prescribing: Same et al. found that antibiotic choice was optimal in 77% of encounters, whereas total duration of therapy was optimal in only 26%, and only 20% of discharge courses were optimal for both choice and duration [121]. Vaughn et al. similarly identified excess duration as a major driver of post-discharge antibiotic overuse, particularly for pneumonia [120]. These findings support the implementation of stewardship tools such as default durations, stop dates, and discharge order sets designed to make guideline-recommended short courses easier to prescribe [50] [53].

The relatively high adherence observed for erysipelas/cellulitis represents a distinctive finding of the present study. Guideline-concordant therapy was documented in 72.0% of cases, and amoxicillin-clavulanate was the only independent protective factor against inappropriate prescribing in the multivariable model. This differs from pediatric ED and urgent care data, where adherence for mild nonpurulent cellulitis was lower [123]. Kovaleski et al. reported 60.0% guideline-adherent prescribing, with non-adherence mainly driven by unnecessary MRSA coverage with clindamycin and inadequate streptococcal coverage with trimethoprim-sulfamethoxazole monotherapy [124]. In our cohort, the higher adherence may reflect a simpler local pathway for mild nonpurulent erysipelas/cellulitis and the frequent use of recommended beta-lactam therapy. This is consistent with IDSA guidance for skin and soft tissue infections, which recommends therapy directed primarily against streptococci for mild nonpurulent cellulitis, reserving MRSA coverage for selected risk profiles [94].

Among antibiotic classes, cephalosporins were the strongest and most consistent marker of inappropriate prescribing. In the overall multivariable model, cephalosporin use was independently associated with guideline-discordant therapy (aOR 7.40, 95% CI 3.88-14.11), and it remained a key predictor in the cystitis and CAP subgroup analyses. This finding is consistent with several strands of the literature. In CAP, Lawless et al. highlighted overuse of ceftriaxone as a major deviation from guideline-based prescribing [122]. In discharge stewardship more broadly, cephalosporins and fluoroquinolones have repeatedly been identified as important classes to monitor during care transitions, particularly because broad-spectrum therapy may be continued after discharge without reassessment [53] [120] .

Combination therapy was independently associated with inappropriate prescribing both in the overall model and in the CAP subgroup. This finding should not be interpreted as indicating that combination therapy is inherently inappropriate. In CAP, regimens such as a beta-lactam plus a macrolide may be appropriate in selected clinical contexts, particularly when atypical coverage is required or when recommended by disease severity and patient risk profile [77] [78]. However, in a discharge cohort including many clinically stable patients, combination therapy may also reflect diagnostic uncertainty or a tendency toward broader empirical coverage at the transition of care. The association between incorrect combination therapy and ED reattendance further suggests that different prescribing errors may have different clinical implications. Future analyses should therefore distinguish unnecessary combination therapy, inadequate atypical coverage, and excessive treatment duration, rather than relying exclusively on a global appropriate/inappropriate classification.

Finally, overall prescribing appropriateness was not significantly associated with ED reattendance or mortality in unadjusted analyses. ED reattendance occurred in 11.7% of patients, and infection-related mortality was 5.4%. This finding aligns with previous studies in which inappropriate or excessive antibiotic prescribing did not clearly translate into lower short-term mortality or readmission rates [120] [122] [124]. This does not mean that inappropriate prescriptions are harmless. Many adverse consequences of antibiotic overuse - including Clostridioides difficile infection, antimicrobial resistance, microbiome disruption, drug-related adverse events, and unnecessary exposure to broad-spectrum agents - may occur outside the measured follow-up window or may not be captured in retrospective ED datasets [3] [4] [53]. Therefore, clinical safety outcomes are important balancing measures, but they should not be the only justification for antimicrobial stewardship at discharge.

Overall, several findings of the present study are consistent with previous literature. First, the high frequency of inappropriate prescribing falls within the range commonly reported in ED and discharge settings, where a substantial proportion of antimicrobial prescriptions has been described as inappropriate or potentially improvable [20] [21] [51] [53] [120]. Second, treatment duration emerged as one of the main weaknesses in prescribing quality, in line with both adult and pediatric studies showing that excessive or non-guideline-concordant duration is a major contributor to antibiotic overuse after discharge [53] [123] [120]. The cystitis findings are also consistent with previous ED-based evidence, which has highlighted frequent diagnostic uncertainty, use of non-first-line agents, fluoroquinolone overuse, and dosing or duration errors in urinary tract infections [90] [91] [119] [121]. Finally, the lack of a clear association between overall prescribing appropriateness and short-term outcomes, such as ED reattendance or mortality, is not unexpected. Similar studies have shown that relevant prescribing-quality gaps may be present even when short-term clinical outcomes do not differ significantly between appropriate and inappropriate prescribing groups [120] [122] [124] .

The present study adds to the literature by providing adult ED-specific data on oral antibiotic prescribing at discharge, a setting that remains less frequently evaluated than inpatient or pediatric discharge prescribing [53] [123]. It also assesses three high-volume infectious syndromes using a component-level definition of appropriateness, including antibiotic choice, dosage regimen, and treatment duration. From a stewardship perspective, the findings identify several practical targets: reducing cephalosporin and fluoroquinolone use in cystitis, improving the appropriateness of CAP combination therapy and treatment duration, preserving the relatively high adherence observed in erysipelas/cellulitis, and embedding default durations into discharge prescribing workflows. Overall, prescribing errors appeared to be more closely related to syndrome, antibiotic class, and treatment structure than to baseline vital-sign instability, supporting the need for targeted decision-support strategies rather than broad educational interventions alone.

Strengths

This study has several strengths. First, it was conducted in a real-world adult ED setting and included a large number of discharge antibiotic prescriptions over a full year. This provides a clinically relevant picture of everyday prescribing practice in an environment characterized by high patient turnover, diagnostic uncertainty, and pressure to make rapid treatment decisions [20] [21].

Second, prescriptions were manually reviewed using predefined clinical criteria and local guideline recommendations. Unlike analyses based only on prescription frequency or antibiotic class, this approach evaluated multiple dimensions of appropriateness, including antibiotic choice, dosage regimen, and duration. This is particularly important because the present study, as well as prior discharge studies, demonstrates that duration errors may be as important as antibiotic selection errors [53] [123] [120].

Third, the study used a syndrome-specific approach. CAP, cystitis, and erysipelas/cellulitis are common ED discharge diagnoses and represent high-yield targets for antimicrobial stewardship interventions. Analyzing them separately made it possible to identify distinct prescribing patterns: cystitis as the highest-priority target, CAP as a syndrome where combination therapy and cephalosporin use require reassessment, and erysipelas/cellulitis as a relatively more standardized pathway.

Fourth, the analysis included both determinants of prescribing appropriateness and clinical outcomes. Although global appropriateness was not associated with ED reattendance or mortality, the identification of cephalosporin use as a predictor of both guideline-discordant prescribing and ED reattendance provides a useful hypothesis for future stewardship and outcome studies.

Finally, the study was grounded in local antimicrobial recommendations adapted to regional epidemiology. This is an important strength because stewardship interventions are most useful when they translate international guidance into feasible local discharge pathways [4] [30] [53].

Limitations

Several limitations should be acknowledged. First, this was a retrospective observational study from a single center. Therefore, the results reflect local prescribing habits, local guidelines, and the organization of the University Hospital of Modena ED, and may not be directly generalizable to other hospitals or healthcare systems.

Second, the definition of appropriateness was based on documentation available in the medical record. In an ED setting, clinical reasoning is not always fully recorded, and some prescriptions classified as inappropriate may have been justified by undocumented factors such as prior microbiology, allergy history, intolerance, patient preference, or follow-up considerations. Conversely, retrospective review may also underestimate inappropriate prescribing when diagnostic uncertainty, lack of symptoms, or unnecessary treatment is not fully captured.

Third, the outcome assessment was limited to ED reattendance and mortality. Other important harms of antibiotic overuse, including Clostridioides difficile infection, allergic reactions, gastrointestinal adverse events, selection of resistant organisms, and patient-reported adverse events, were not systematically measured. Therefore, the lack of association between appropriateness and short-term outcomes should not be interpreted as evidence that inappropriate prescribing is clinically irrelevant [3] [4] [53].

Fourth, the analysis focused in detail on selected infectious syndromes and did not fully explore all other infections for which antibiotics were prescribed at discharge. Therefore, the results mainly apply to community-acquired pneumonia, cystitis, and erysipelas/cellulitis, which were chosen because of their frequency and stewardship relevance.

Finally, the sample size of some subgroups was limited, particularly for erysipelas/cellulitis. This may have reduced the power to detect predictors of inappropriate prescribing and may explain why some strong univariate associations did not remain significant after multivariable adjustment.

12. CONCLUSIONS

In conclusion, inappropriate oral antibiotic prescribing at ED discharge remains frequent and clinically relevant, affecting more than half of reviewed prescriptions and nearly 60% of prescriptions for the three target syndromes. The main gaps were not primarily related to baseline clinical instability, but to syndrome-specific prescribing patterns, antibiotic class selection, combination therapy, and treatment duration.

Cystitis represented the most critical stewardship target because it combined high frequency, low guideline concordance, and strong associations with cephalosporin and fluoroquinolone use. CAP also showed substantial room for improvement, particularly in relation to cephalosporin use, combination therapy, and duration. In contrast, mild erysipelas/cellulitis showed the highest adherence, suggesting that simpler and more standardized local pathways can improve prescribing behavior at discharge.

These findings support the development of ED-specific antimicrobial stewardship interventions focused on discharge prescriptions. Practical measures should include syndrome-specific order sets, default short durations, prompts discouraging inappropriate cephalosporin and fluoroquinolone use, structured reassessment of combination therapy, and selective infectious disease or pharmacist review for high-risk prescriptions. Future research should evaluate whether these interventions reduce unnecessary antibiotic exposure without increasing ED reattendance, treatment failure, or mortality, and should include patient-centered harms such as adverse drug events and Clostridioides difficile infection.

Overall, this study adds adult ED-specific evidence to the growing literature on discharge antibiotic stewardship and identifies concrete, measurable targets for improving the quality of antibiotic prescribing at the transition from emergency care to the community.

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