





Inappropriate Use of Antimicrobials for Lower Respiratory Tract Infections in Elderly Patients: Patient- and Community-Related Implications and Possible Interventions

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Abstract The elderly are more susceptible to infections, which is reflected in the incidence and mortality of lower respiratory tract infections (LRTIs) increasing with age. Several aspects of antimicrobial use for LRTIs in elderly patients should be considered to determine appropriateness. We discuss possible differences in microbial etiology between elderly and younger adults, definitions of inappropriate antimicrobial use for LRTIs currently found in the literature, along with their results, and the possible negative impact of antimicrobial therapy at both an individual and community level. Finally, we propose that both antimicrobial stewardship interventions and novel rapid diagnostic techniques may optimize antimicrobial use in elderly patients with LRTIs.

Key Points

Reports on (in)appropriate antimicrobial use lack a reference standard for defining and measuring appropriateness of treatment.

Quinolones or macrolides should be restricted to selected cases empirically, given the low incidence of atypical pathogens in elderly patients and higher risks of adverse drug events and drug–drug interactions.

The use of low-dose computed tomography scanning, point-of-care ultrasonography, or point-of-care polymerase chain reaction testing for viral pathogens are promising research areas to decrease the inappropriate use of antimicrobials.

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1 Introduction

Elderly people (adults over 65 years of age) comprised one-fifth of the total population in Europe in 2016, and this proportion may further increase to 25% in 2030 [1, 2]. The elderly are more susceptible to infections and their sequelae than younger adults [3, 4], which is reflected in the incidence and mortality of lower respiratory tract infections (LRTIs) increasing with age [5–7]. Next to increased incidences of comorbidities, it is thought that age-related altered immune regulation, often referred to as ‘immunosenescence’, also contributes to this [8]. Several aspects of LRTIs in the elderly make it increasingly

difficult to determine the most appropriate antimicrobial therapy for individual patients. First, the etiology of LRTIs in elderly patients could be slightly different compared with younger adults, which would require adjusted empirical antimicrobial therapy. In addition, the diagnosis of LRTIs in the elderly could be more challenging, which might lower the threshold for prescribing antimicrobials. Furthermore, with advancing age, the human body changes in composition and organ function, resulting in alteration of the pharmacokinetics and pharmacodynamics of antimicrobials [9]. When combined with the increasing frequency of comorbidities and/or polypharmacy, this facilitates the occurrence of adverse drug events (ADEs) and drug–drug interactions (DDIs).

We discuss the etiology, currently used definitions for appropriate use of antimicrobials, and different negative consequences of antimicrobial therapy for LRTIs in elderly patients, in both individual patients and the community. Finally, we propose targeted interventions to improve antimicrobial prescribing in these patients.

2 Microbiological Etiology

Seven studies, all from Europe, have made head-to-head comparisons of etiology in elderly and younger adult patients with LRTIs [10–16]. A cut-off of 65 years of age was used to define categories. The ranges of the most

commonly identified pathogens are summarized in Table 1; *Streptococcus pneumoniae* was the most frequently identified pathogen in both age groups. The most discernible differences between the two groups were that Gram-negatives, especially Enterobacteriaceae, were found more frequently in the elderly, whereas certain atypical pathogens (*Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Coxiella burnetii*) were more frequent in younger patients. Increasing age and nursing-home residency are associated with colonization of Gram-negative bacteria in the oropharynx. Microaspiration is considered an etiologic pathway in the development of LRTIs in elderly patients, which could explain the increase in Gram-negatives [10, 17, 18]. The lower prevalence of atypical pathogens in the elderly may be caused by less-frequent exposure to risk factors [10].

Higher incidences of viral pathogens in elderly patients have been reported [12, 14, 16], although this was not demonstrated consistently [10, 11, 15]. Studies showing higher incidences of viral pathogens were mostly population-based, including outpatients from general practitioners, while contradicting studies were hospital-based, which may explain conflicting results. In addition, bias could have been introduced because viral testing was not uniformly performed and age may have influenced the decision to test [19]. Two recent cohort studies of hospitalized community-acquired pneumonia (CAP) patients, one from the US ($N = 2259$) and one from The Netherlands ($N = 408$),

Table 1 Identified causal pathogen in studies with head-to-head comparison between younger and elderly patients

Pathogens	Young patients ^{a,c} (%)	Elderly patients ^{b,c} (%)	References
<i>Streptococcus pneumoniae</i>	9–35	8.6–36	[10–16]
<i>Staphylococcus aureus</i>	0.3–4	0.0–5	[11–13, 15, 16]
<i>Haemophilus influenzae</i>	1–2	0.7–10	[10–13, 15, 16]
Gram-negatives	0–7	1.4–15	[10–13, 15]
Enterobacteriaceae	0.4–1.3	0.9–2.6	[13, 16]
Atypical pathogens	11–37	1–15	[10, 11, 13–15]
<i>Legionella pneumophila</i>	3.4–5.2	1–5	[10–16]
<i>Mycoplasma pneumoniae</i>	2.8–15	0–3.2	[10–16]
<i>Coxiella burnetii</i>	0.7–15.8	0–3.5	[10, 13–15]
<i>Chlamydia pneumoniae</i>	0.1–8.2	0–6.7	[10, 12–16]
Total viral pathogens	3.6–4	4.5–13.4	[10, 11, 14, 15]
Influenza	1.2–3.0	0.3–4.8	[10, 12, 14–16]
Parainfluenza	1.3	1–8.6	[10, 14]
Respiratory syncytial virus	0.0–0.4	0.7–1.8	[10, 12, 15]
Unknown	24–79	40–80	[10–16]

^aLess than 65 years of age, except van Vught et al. [11] (< 50 years of age). The paper by Fernández Sabé et al. [10] has been excluded for this specific younger age group as their cut-off was 80 years of age; otherwise this younger age group also included patients aged 65–80 years

^bLess than 65 years of age; however, exceptions are Fernández Sabé et al. [10] (> 80 years of age) and Van Vught et al. [11] (> 80 years of age)

^cA range of reported prevalences of pathogens were found in the literature

routinely performed testing and found a virus as the only pathogen in 22% and 13% of cases, respectively. In both studies, the most commonly detected viral pathogens were human rhinovirus and influenza virus [20, 21].

The occurrence of a viral etiology was similar for young and elderly patients in the US study [20], while the study from The Netherlands found even more viral pathogens with increasing age. [21] The contribution of viral pathogens as a cause for CAP in all age groups might be larger than previously thought.

Elderly patients more often had unknown etiology in LRTIs compared with younger adults [10, 11, 13, 15, 16]. Possible reasons for less detection of the causal pathogen could be a more conservative diagnostic approach in this group of patients or difficulty in obtaining good-quality material for culturing [13].

In recent years, healthcare-associated pneumonia (HCAP) has been proposed as a separate entity from CAP. HCAP may be more frequently caused by gram-negatives and multidrug-resistant organisms (MDROs), and is associated with higher mortality [22–25]. However, a meta-analysis of 24 studies concluded that HCAP criteria do not accurately predict MDROs, although low study quality and heterogeneous designs preclude a firm conclusion [22]. European studies tend to report community-like etiology, while studies from Asia and the US show increased MDRO rates in HCAP patients [25–28]. To date, the clinical relevance of HCAP remains unclear [23, 24]. In fact, both Infectious Diseases Society of America (IDSA) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines do not address HCAP, which leaves a gap in the recommendations regarding treatment for patients from long-term care facilities (LTCFs).

The microbial etiology does not justify routine empirical coverage of *Legionella pneumophila* as the low incidence is further decreased in elderly patients to approximately 1–5% (Table 1). As members of our group have previously suggested, β -lactam monotherapy, preferably aminopenicillins, should generally be the first choice of empirical therapy [29, 30]. Naturally, the severity of disease, local epidemiologic data, prior cultures or known colonization of individual patients, comorbidities, or allergies could lead to an alternative antibiotic choice. Doxycycline, the addition of a macrolide to β -lactam therapy, or the newer fourth-generation fluoroquinolones are potent therapies, but higher risks of ADEs and DDIs should be considered.

3 Inappropriate Use of Antimicrobials

Whether to start antimicrobial therapy for LRTIs, and choosing the specific class, depends on multiple factors in daily clinical practice. Most factors in this decision

pathway are dependent on clinical judgement, which interferes with evaluating appropriateness in a standardized way. Deviation from protocol for empirical therapy, definitive drug selection, and duration of therapy might be justifiable for individual patients, for reasons that are not captured in the guidelines.

These difficulties are also reflected in the different definitions of (in)appropriate antimicrobial therapy found in the literature. Some studies have assessed (in)appropriate antimicrobial therapy by evaluating empirical therapy and/or definitive drug selection through expert opinion [31–36]. Others have aimed at the appropriateness of diagnosis, dosage, route of administration, or duration of antimicrobial therapy [37–41]. A less subjective method to assess appropriateness is to evaluate therapy according to in vitro susceptibilities, yet this requires positive microbiological testing results and cannot be solely relied on [31–34, 36]. Another method focuses on costs, defining inappropriateness as unnecessary use of combination therapy with the same spectrum [42]. Lastly, the indication for starting antimicrobial therapy, i.e. unnecessary antimicrobial therapy, can be evaluated, where inappropriateness seemed to increase with age [43]. The (in)appropriateness criteria for several studies specifically addressing antimicrobials for LRTIs in elderly patients are summarized in Table 2. Generally, the proportion of appropriate antimicrobial treatment ranged from 60 to 80%. Although none of these studies found an association with increasing age, it has been suggested that both nursing-home or LTCF residency and polypharmacy, all occurring more frequently with advancing age, increase the risk for inappropriate prescriptions [44]. For example, the point prevalence of antimicrobial use in nursing homes is approximately 10%, and the proportion of prescribed antimicrobial courses deemed unnecessary or inappropriate after post hoc review ranged from 20 to 75% [45–50].

It is clear that a reference standard for measuring inappropriate antimicrobial use is currently lacking, which was also concluded by a specific review of this subject [51]. More work on definitions and standardization is heavily needed to ensure evaluation of appropriateness will become more reliable and less dependent of the interobserver variation inherent to expert evaluation [52].

Although it has been suggested that certain potential inappropriate prescriptions could be automatically recognized by an electronic health records system, we think this is unfeasible as human judgement is almost always needed [53]. For example, a patient with a documented allergy to guideline-recommended treatment could be automatically flagged by such a system as appropriate deviation, yet this is dependent on accurate interpretation and registration of allergy data, with the latter often being incorrect [54].

Despite the heterogeneity in definitions, and resulting heterogeneity in inappropriateness rates, there is a clear

Table 2 Examples from the literature of different definitions of (in)appropriate antimicrobial use for LRTIs in the elderly

Setting	Definition of inappropriate antimicrobial use	Appropriateness of RTI treatment	References
Tobia et al., 2008 Outpatients at emergency department [N = 153]	Medication Appropriateness Index (MAI) 1. Indication (e.g. presence of symptoms) 2. Effectiveness 3. Dosage 4. Directions (e.g. route) 5. Practicality (e.g. adherence) 6. Drug–drug interactions 7. Drug–disease interactions 8. Unnecessary duplication 9. Duration 10. Expensiveness (least expensive alternative) Rating A, appropriate; B, marginal; C, inappropriate	n = 99 (65%)	[93]
Van Buul et al., 2015 Long-term care facility [N = 208]	Algorithm for RTI based on guidelines and national expert panel Distinction between: (1) acute cough; or (2) no acute cough but fever; or (3) no cough and fever Then presence/absence of abnormalities on lung auscultation, COPD, CRP results, other airway and non-airway symptoms, and certain risk factors Rating A, appropriate; B, probably appropriate; C, probably inappropriate; D, inappropriate; E, insufficient information	n = 180 (86.5%; range 60.0–96.2)	[41]
Vergidis et al., 2011 Long-term care facility [N = 752]	Appropriate (with/without antimicrobial prescription) With: when effective drug was used Without: when use of an antimicrobial was not indicated Inappropriate With: when a more-effective drug was indicated Without: undefined Unjustified With: use of any antimicrobial was not indicated Without: when use of an antimicrobial was indicated Insufficient information for categorization	n = 592 (79%)	[50]
Loeb et al., 2001 Long-term care facility [N = 646]	Assessment of prescriptions to see if they fulfilled the diagnostic criteria At least three of the following: (1) new/increased cough; (2) new/increased sputum production; (3) fever; (4) pleuritic chest pain; (5) new or increased physical findings on chest examination; (6) new/increased shortness of breath or respiratory rate more than 25/min, or worsening mental or functional status	n = 375 (58%)	[49]

LRTIs lower respiratory tract infections, RTI respiratory tract infection, COPD chronic obstructive pulmonary disease, CRP C-reactive protein

consensus on the adverse consequences of inappropriate antimicrobial use at the patient and community level [55, 56]. Both will be addressed in the following section.

4 Negative Impact of Antimicrobials in the Elderly

Treating patients with antimicrobials is not without risk. Antimicrobials can have a negative impact on both individual users and the community. For individuals, there is a

risk of different ADEs, including DDIs and drug–comorbidity interactions. In elderly patients, the age-related changes in pharmacokinetics, frequent concurrent use of medication, and higher prevalence of comorbidities, all contribute to an increased risk of such events. Faulkner et al. provide an extensive review of antimicrobial ADEs in the elderly [57]. In the community, there is a risk of spread of *Clostridium difficile* infections (CDIs) and antimicrobial resistance.

4.1 Adverse Drug Events (ADEs)

In a cohort study evaluating antimicrobial-associated ADEs in hospitalized patients ($N = 1488$; median age 59 years), 20% of patients experienced at least one ADE, with gastrointestinal, renal, and hematologic abnormalities being the most frequent. Furthermore, 20% of the reported antimicrobial-related ADEs were due to unnecessary antimicrobial use [58]. In another cohort evaluating ADEs in nursing-home residents, antimicrobials were the second most often reported drug class to cause an ADE (20%), after antipsychotics. The majority of observed ADEs were rashes and CDIs [59].

Certain ADEs are serious enough that elderly patients have to visit the emergency room (ER); 10.6% of elderly patient ER visits were due to an ADE, with antimicrobials being one of the most frequently implicated medication classes (16.7% of all ADEs, and 25% of definite or probable ADEs) [60]. The most frequent (serious) ADEs in elderly patients who use β -lactam antimicrobials for LRTIs are drug fever, interstitial nephritis, and blood dyscrasias. For patients who use macrolides, the most frequent ADE is QT prolongation, while for patients taking trimethoprim-sulfamethoxazole, the most frequent ADEs are hyperkalemia, blood dyscrasias, and drug fever [57]. Certain very rare ADEs, such as tendinitis and tendon rupture during fluoroquinolone use, are relatively more frequent in the elderly and can be further increased by concomitant glucocorticoid use or renal failure [61, 62], although the absolute risks remain low [61].

4.2 Drug–Drug Interactions

The elderly have an increased risk for DDIs since polypharmacy is more frequent [4]. It is estimated that 51% (1380/2707) of elderly patients receive six or more drugs per day [63]. The most serious DDIs in elderly patients using antimicrobials for LRTIs are trimethoprim-sulfamethoxazole in combination with vitamin K antagonists (increases anticoagulant effect), trimethoprim-sulfamethoxazole with potassium-sparing diuretics (risk of hospitalization due to hyperkalemia), and clarithromycin/erythromycin with drugs that are deactivated by cytochrome P450 3A4 enzymes (e.g. risk of rhabdomyolysis by increased concentrations of atorvastatin) [57].

4.3 Drug–Comorbidity Interactions

Macrolides are associated with an increased risk for cardiovascular events and deaths, especially in (elderly) patients with a higher baseline risk for cardiovascular events [64–69]. These associations should caution the use of macrolides for LRTIs unless strictly necessary. Renal

insufficiency is more frequent in the elderly, which results in a decreased elimination of certain (hydrophilic) antimicrobials (e.g. cephalosporins, fluoroquinolones) and increases the risk of ADEs. Therefore, a dose adjustment is recommended for patients with impaired renal function [9, 70].

4.4 Clostridium Difficile Infection

Broad-spectrum antimicrobials disturb the gastrointestinal flora, contributing to an increased risk of CDIs. Increased age, recent hospitalization, immune suppression, malignancy, chronic renal failure, and use of proton pump inhibitors have been identified as independent risk factors of CDIs and are highly prevalent in the elderly [70, 71]. Macrolides are more strongly associated with CDIs than doxycycline, and physicians may therefore choose the latter when atypical coverage is deemed necessary [70]. Still, the risk of developing CDIs with macrolides appears smaller than with fluoroquinolones, clindamycin, or broad-spectrum β -lactams [72].

4.5 Antimicrobial Resistance

There is clear consensus that inappropriate antimicrobial use contributes to antimicrobial resistance, potentially leading to increased morbidity, mortality, and healthcare costs [73, 74]. Antimicrobial resistance rates may increase with age, as reported in a Canadian surveillance study, further increasing the risk for the elderly population [75]. This could be explained by elderly people more often residing in LTCFs, needing hospitalization, receiving healthcare at home, and receiving antimicrobials, which are all risk factors for developing antimicrobial resistance [70].

5 Optimizing Appropriate Antimicrobial Use in Elderly Patients

5.1 Antimicrobial Stewardship Interventions

Antimicrobial stewardship interventions aim at reducing inappropriate use of antimicrobials while maintaining good clinical outcomes. Elderly patients might especially benefit from antimicrobial stewardship as they may have the highest risk for worse clinical outcomes due to both overtreatment (e.g. antimicrobial side effects, CDIs) or undertreatment (e.g. infectious complications). The risk for and possible harm due to treatment differs per patient and depends on patient factors such as comorbidities, immunological status, comedication, previous antibiotic treatment, recent hospitalizations, and the severity of the LRTI. Therefore, an individualized approach where

individual patient risks are balanced with possible collateral damage in the form of selecting for antimicrobial resistance is recommended.

Commonly used antimicrobial stewardship interventions include periodic or individual patient audits and feedback, decision support, education (educational meetings, educational materials), and formulary restriction of antimicrobials [73, 76].

To date, the majority of studies on stewardship interventions are performed on adult or pediatric patients, or on specific hospital settings, e.g. intensive care unit (ICU). In a recent systematic review of stewardship interventions in hospitalized patients, only 1.8% (4/211) of studies specifically targeted elderly patients [73, 77–80]. Two controlled before–after studies showed a reduction in 30-day mortality after introducing a pneumonia guideline with clinical decision support [77, 78]. Two interrupted time series showed a reduction in the incidence of CDIs after implementation of an audit and feedback program and a restrictive antimicrobial policy [79, 80]. Although promising, these four studies used non-randomized designs, risking confounding bias. There is a great need for high-quality studies in elderly patients. Currently, the effects of antimicrobial stewardship interventions in elderly patients may be over- or underestimated.

As stated earlier, the appropriate prescription of antimicrobials in LTCFs is often impeded by the frailty of elderly residents, limited clinical evaluation, sometimes only consisting of a nurse's assessment and telephone supervision by a physician, and lack of diagnostic testing. In nursing homes, the majority of antimicrobials are prescribed after telephone contact with nursing staff, highlighting the importance of involving nurses in antimicrobial stewardship programs [81]. In a recent review of stewardship interventions in LTCFs, the following approaches were identified to be the most effective: multidisciplinary education; pre-prescriptive data collection tools; post-prescriptive prescriber recommendations; and introducing consultation by infectious diseases experts [82]. When designing antimicrobial stewardship interventions, it is important to consider the setting and corresponding prescription process. This was illustrated in nursing-home interventions designed to improve communication, which were only effective in reducing antimicrobial use when nursing staff were involved [83, 84]. Appealing antimicrobial stewardship targets to improve antimicrobial use for LRTIs in LTCFs include improving the indication for starting antimicrobials, optimizing the use of available diagnostics, limiting the use of fluoroquinolones given their strong association with CDIs, and ensuring proper dosing and duration of antimicrobial therapy [83, 85].

5.2 New Diagnostic Techniques

5.2.1 Imaging

As infections can be difficult to diagnose in elderly patients, they may be initially treated with broad-spectrum antimicrobials. Novel diagnostic techniques to establish the diagnosis of LRTIs may particularly reduce unnecessary antimicrobials in elderly patients. The current cornerstone for the radiological diagnosis of pneumonia is the demonstration of an infiltrate by conventional chest X-ray; however, the estimated sensitivity of a chest X-ray is only 60–70% in patients with a clinical diagnosis of CAP [29, 86, 87]. In addition, certain comorbidities that are common in elderly patients (e.g. heart failure and chronic obstructive pulmonary disease) may impede the detection of pulmonary infiltrates [88]. The increasing availability of computed tomography (CT) scans and the possibility of low- or ultra-low-dose scanning seems a promising alternative. Recently, CT scans changed the diagnosis of 58.6% (95% confidence interval 53.2–64.0%) of consecutive CAP patients, potentially leading to optimization of management in 25% of patients [89]. These results need to be validated in clinical practice to demonstrate improved patient outcomes, while reducing antimicrobial use for non-infectious alternative diagnoses. In settings where CT scans are not readily available, chest ultrasonography may be a valuable alternative. It has high diagnostic accuracy for pneumonia, can be performed at the bedside, is highly reproducible in trained professionals, and the costs are relatively low [90].

5.2.2 Microbiological Testing

Established microbiological techniques to determine the causative pathogen include respiratory cultures or polymerase chain reaction (PCR), blood cultures, and urinary antigen tests for *Legionella* and pneumococcus; however, the sensitivity of these tests are limited and in 60–70% of patients suspected of CAP no causative pathogen will be identified [20, 29].

When viral CAP is suspected, point-of-care PCR (PoC-PCR) for respiratory viruses might play a role in optimizing antimicrobial therapy. Previous studies using regular respiratory PCR have failed to show an effect on antimicrobial use, possibly because it is difficult to stop antimicrobials after they have been administered for 1–2 days when PCR results become available [91, 92]. PoC-PCR may allow withholding or rapid discontinuation of antimicrobials if a viral pathogen is identified as results can be available in 1–2 h. The effects and cost effectiveness of PoC-PCR on antimicrobial use and patient outcome have not yet been investigated, but a cluster randomized clinical

trial evaluating the clinical effects of both low-dose CT and PoC-PCR in patients with CAP admitted to a non-ICU ward is underway (ClinicalTrials.gov identifier: NCT01660204).

6 Conclusions

We have addressed several issues on the appropriate use of antimicrobials in elderly patients with LRTIs. As the microbial etiology is only slightly different compared with the younger population, the mainstay of treatment should consist of β -lactam monotherapy. Extended coverage of gram-negatives could be considered in LTCF or nursing-home residents. Quinolones or macrolides should be restricted to selected cases empirically, given the low incidence of atypical pathogens in elderly patients and higher risks of ADEs and DDIs. Next to these ADEs, inappropriate use of antimicrobials contributes to CDIs and antimicrobial resistance. A reference standard for measuring inappropriate antimicrobial use is currently lacking. Future work on definitions and standardization will hopefully increase validity and generalizability of reports on (in)appropriate antimicrobial therapy. Well-designed antimicrobial stewardship interventions could improve antimicrobial prescribing, but studies specifically targeting elderly patients are needed. These programs should generally consist of multiple components, depending on the specific clinical setting, such as improving diagnostics (i.e. indication for starting antimicrobials) and ensuring proper dosing and duration of therapy. We argue that new diagnostic techniques such as low-dose CT scanning or PoC-PCR testing for viral pathogens could potentially reduce inappropriate use of antimicrobials. Such techniques and interventions can hopefully decrease the inappropriate use of antimicrobials in the near future.

Compliance with Ethical Standards

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Conflicts of interest Inger van Heijl, Valentijn A. Schweitzer, Lufang Zhang, Paul D. van der Linden, Cornelius H. van Werkhoven, and Douwe F. Postma declare that they have no conflicts of interest.

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