Chapter

Pneumonia: Drug-Related Problems and Hospital Readmissions

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Abstract

Pneumonia is one of the most common infectious diseases and the fourth leading cause of death globally. According to US statistics in 2019, pneumonia is the most common cause of sepsis and septic shock. In the US, inpatient pneumonia hospitalizations account for the top 10 highest medical costs, totaling $9.5 billion for 960,000 hospital stays. The emergence of antibiotic resistance in the treatment of infectious diseases, including the treatment of pneumonia, is a globally alarming problem. Antibiotic resistance increases the risk of death and re-hospitalization, prolongs hospital stays, and increases treatment costs, and is one of the greatest threats in modern medicine. Drug-related problems (DRPs) in pneumonia - such as suboptimal antibiotic indications, prolonged treatment duration, and drug interactions - increase the rate of antibiotic resistance and adverse effects, thereby leading to an increased burden in treatment. In a context in which novel and effective antibiotics are scarce, mitigating DRPs in order to reduce antibiotic resistance is currently a prime concern. A variety of interventions proven useful in reducing DRPs are antibiotic stewardship programs, the use of biomarkers, computerized physician order entries and clinical decision support systems, and community-acquired pneumonia scores.

Keywords: Pneumonia, drug-related problems, re-hospitalization, prescriptions, interventions

1. Introduction

Pneumonia is an acute lower respiratory tract infection caused by bacteria, viruses, or fungi. Groups of patients at high risk of getting pneumonia include children under 5 years old, people over 65 years old, and people with comorbidities. Pneumonia is the leading cause of death in children, and among the top four causes of death globally [1]. Each year, pneumonia kills more than 800,000 children under the age of 5, equivalent to about 2,200 children every day [2]. In the United States, the annual incidence of community-acquired pneumonia (CAP) was 248 cases per 100,000 persons [3]. A study in central Vietnam reported that the incidence of CAP

in subjects aged ≥ 65 years was 4.6 per 1,000 person-years (95% CI, 3.8–5.5) [4]. Hospitalized patients diagnosed with pneumonia accounted for 19.9%, 6.4%, and 1.5% in the Philippines, Malaysia, and Indonesia, respectively. The total estimated costs incurred for pneumonia patients were in Malaysia 4.1 million USD, in Indonesia 2.6 million USD, and in the Philippines 2.6 million USD [5].

Drug-related problems are defined as 'events or circumstances involving drug therapy that actually or potentially interfere with desired health outcomes' [6]. Causes of DRPs can be related to inappropriate drug selection, inappropriate dosage, duration of use of medication longer or shorter than recommended, incorrect drug use processes, or poor compliance, all resulting in decreased treatment effectiveness and increased morbidity and mortality [7–9]. In Ethiopia, the proportion of patients hospitalized for infectious diseases, and who also had DRPs, was 71.51% (123/172); of these, the unnecessary broad-spectrum antibiotic option ceftriaxone accounted for 44.77% [10]. Similarly, in a study in Spain, almost half (45.1%) of hospitalized patients suffered from DRPs [11]. Common DRPs associated with pneumonia include inappropriate antibiotic indications, prolonged antibiotic treatment, and overtreatment, which may lead to potential drug–drug interactions [12–15]. In the context of increasing antibiotic resistance, prescribing doctors, often concerned about possibly missing pathogenic bacteria, tend to prescribe broad-spectrum antibiotics over a longer treatment time to avoid recurrence of the disease. Fear, rather than lack of knowledge, is a major barrier to preventing overtreatment with antibiotics [16]. Therefore, a new method being considered for improving empirical antibiotic selection is the community-acquired pneumonia score. This score can be used in a prediction model of clinical data, enabling more accurate application of empirical antibiotics [17]. In addition, many intervention tools need to be applied, such as antibiotic management programs, biomarkers, and computerized physician order entries (CPOE), to ensure the effectiveness and safety of guideline compliance. The computerized physician order entry (CPOE) and clinical decision support systems (CDSS) are valuable technological tools for use in interventions to prevent adverse drug events (ADEs). However, in the healthcare system, the role of the clinical pharmacist in minimizing DRPs remains crucial [14]. The chapter is, therefore, to summarize an overview of DRPs in pneumonia and recommend some strategies for reducing these DRPs.

2. Drug-related problems in pneumonia

2.1 Improper drug selection and dose selection

Prescribing inappropriate antibiotics leads to increased mortality, the development of antimicrobial resistance, and added treatment costs [18, 19]. Meta-analysis of 7401 patients with ventilator-associated pneumonia (VAP), using unadjusted data, revealed that inappropriate antibiotic therapy significantly increased the mortality of patients (odds ratio [OR], 2.34; 95% CI, 1.51–3.63; P = 0.0001, I2 = 28.5%) [8]. A retrospective cohort study of bacteremic pneumonia, conducted in Barnes-Jewish Hospital in Missouri, USA (2008–2015) using multivariable logistic regression analysis for hospital mortality, indicated that inappropriate initial antibiotic treatment had the greatest odds ratio with mortality (OR 2.2, 95% CI 1.5–3.2, P < 0.001). The rate of inappropriate antibiotic initiation was significantly higher in patients with ceftriaxone-resistant pathogens than with ceftriaxone-susceptible pathogens (27.9% vs. 7.1%, P < 0.001), and the associated hospital mortality rates were respectively 41.5% vs. 32.0% (P = 0.001) [9].

Inappropriate antibiotic selection is one of the most common DRPs in patients with pneumonia, and particularly community-acquired pneumonia (CAP). Antibiotic prescriptions collected from 22 pharmacies in Mongolia indicated that inappropriate drug selection affected both adults (57.7%) and children (56.6%) [20]. A study among 518 outpatients with CAP in the Veterans Affairs Western New York Healthcare System indicated that 69% of patients received an inappropriate antibiotic; for 76.7% of them an incorrect drug had been prescribed, based on the patient's comorbidities [21]. In Thailand, a prospective observational study of severe CAP in general medical wards showed that 52% of patients received initial antibiotic regimens that were discordant with IDSA/ATS guidelines [22].

The increase in resistance rates of bacteria to antibiotics leads to inappropriate selection of initial antibiotics. Due to an "encirclement" mentality, doctors often tend to choose empiric broad-spectrum antibiotics; this invisible cause increases antibiotic resistance, resulting in a "vicious circle" that increasingly burdens patients and society [23–25]. In particular, prescribing broad-spectrum antibiotics for a low-risk group increases the risk of unwanted effects rather than making treatment beneficial. According to current guidelines for the treatment of community-acquired pneumonia, an outpatient should receive beta-lactam or a macrolide or doxycycline [26, 27]. A retrospective chart review at a large hospital indicated that fluoroquinolones were antibiotics overprescribed for 71% of patients in the low-risk group [28]. Another retrospective chart review among 156 adult patients with a diagnosis of CAP, admitted to a community hospital emergency department in Canada, found that physicians overprescribed fluoroquinolones for 80.8% of patients who did not need them [29]. Over-prescribing of fluoroquinolones for outpatients with pneumonia increases the risk of side effects: tendon rupture, tendonitis, feeling shaky, unusual hunger, serious events of aortic ruptures or tears, and development of antibiotic resistance [30–32].

For this reason, antibiotic stewardship programs (ASPs) and clinical pharmacists play an important role in promoting the appropriate prescribing of empiric antibiotics. A retrospective cohort study of patients with CAP indicated a significant reduction in fluoroquinolone prescribing over time following intervention involving ASPs and clinical pharmacists [33]. An additional new method for improving empirical antibiotic selection is the community-acquired pneumonia score. This score provides a model of clinical data, thereby enabling the proper use of empirical antibiotics [17]. Implementation of an empiric therapy guide is important to minimize DRPs in the initial selection of antibiotics for pneumonia, as the causative organism and the patient's susceptibility to it are often unknown at the time of prescription. Galanter KM et al. demonstrated that after intervention in accordance with the empiric therapy guide, the rate of broad-spectrum antibiotic indication for CAP decreased significantly, by 17.0% [34].

In Canada, a study on pneumonia showed that prescribed antibiotic doses tended to be higher than recommended [29]. In contrast, a prospective multinational study involving 68 ICUs across 10 countries confirmed that 20% of patients received less than the most conservative PK/PD target (50% f T > MIC), and fewer than 50% of patients received a preferred PK/PD target (100% f T > MIC) [13]. Such insufficient antibiotic exposure can also facilitate antibiotic resistance. For the treatment of CAP, especially critical patients require individualized dosing based on the severity of disease, local documented pathogen susceptibilities, and causal bacteria. Patient characteristics also play an important role in reducing mortality.

2.2 Drug interactions

Pneumonia patients often have not just one diagnosis but suffer from comorbid conditions. Frequent comorbidities are diabetes mellitus, cerebrovascular disease, chronic lung disease, chronic kidney disease, and dementia [15, 35, 36]. Common medication classes used for the management of comorbid conditions are cardiovascular agents, alimentary tract and metabolism agents, nervous system agents, respiratory agents, blood-forming agents, and general anti-infective agents for systemic use. The potential of drug–drug interactions in cases of pneumonia is more prevalent in older patients, possibly leading to chronic diseases and polypharmacy; some drugs even increase the risks of pneumonia [37]. In pneumonia patients, comorbidities have been strongly associated with long-term mortality [36], and concurrent use of multiple drugs can lead to an increased risk of drug–drug interactions (DDIs) [15, 35, 38]. Results of a study in a population, most of whom were concurrently using >10 drugs, revealed that 73.1% of these patients faced potential DDIs. Indeed, more than half of the patients presented with major potential DDIs [15]. Furthermore, nearly 75% of patients with community-acquired pneumonia (CAP) were subjected to polypharmacy [35].

Some clinical consequences of DDIs included increased or decreased therapeutic effectiveness, adverse drug reactions (ADRs), and toxicity (nephrotoxicity, hepatotoxicity) [15, 38]. DDIs can take place between different antibiotics, and between antibiotics and other medications. For treating pneumonia many guidelines recommend using β-lactams, macrolides, and fluoroquinolones. This may cause a prolonged QT interval (when fluoroquinolones or macrolides are administered) or a prolonged Prothrombin Time and International Normalized Ratio (INR) (if fluoroquinolones and warfarin are administered concurrently) [37]. Therefore, to prevent the negative effects of polypharmacy, consultations should be held to identify potential DDIs and alert physicians. Moreover, medical staff should refer to more than one drug interaction checker tool -- like Lexi-Interact, Micromedex, Medscape, Drugs.com. -- as well as adhere to guidelines for optimizing the use of prescribed drugs and discontinuing the use of unnecessary drugs.

2.3 Initiation and duration of administration antibiotic treatment

Patients whose initial appropriate antibiotics therapy is delayed may have increased morbidity rates compared to those receiving appropriately prescribed therapy on time. A systematic review in patients hospitalized with infections due to *Klebsiella pneumoniae* or *Escherichia coli* found that a delay in appropriate antibiotic therapy of more than 24 hours and 48 hours after culture collection, or in culture and susceptibility reporting, can increase the risk of mortality: OR 1.60 (95% CI, 1.25–2.50) and OR 1.76 (95% CI, 1.27–2.44) respectively [39]. A prospective cohort study in patients with VAP showed that for thirty-three patients (30.8%) the appropriate antibiotic treatment was delayed for >24 hours after they first met the diagnostic criteria for VAP; this initially delayed appropriate antibiotic treatment was a risk factor for increasing the hospital mortality rate (adjusted odds ratio, 7.68; 95% CI 4.50 to 13.09; $p < 0.001$) [40].

The British Thoracic Society Guidelines for the Management of Community-Acquired Pneumonia in Adults recommends the administration of antibiotics within four hours of admission to hospital for adults with radiologically confirmed CAP [41]. A large study (n = 13,725 from 188 institutions) conducted among adults hospitalized with CAP indicated that 37% of patients failed to receive antibiotics within four hours of admission. Delay time of the first antibiotic was associated with a greater OR of 30-day inpatient mortality. The adjusted 30-day inpatient

mortality was lower for adults who received their initial antibiotic within four hours, compared with >4 hours (adjusted OR 0.84, 95% CI 0.74 to 0.94; p = 0.003) [42]. A retrospective study (n = 18,209) of Medicare patients older than 65 years who were hospitalized with CAP revealed that 39.1% did not receive antibiotics within four hours of admission. Initial administration of antibiotics within four hours, versus more than four hours, after arrival at the hospital was associated with reduced in-hospital mortality (6.8% vs. 7.4%; adjusted odds ratio (AOR)), 0.85; 95% CI, 0.74–0.98), versus mortality within 30 days of admission (11.6% vs. 12.7%; AOR, 0.85; 95% CI, 0.76–0.95), and length of stay exceeding the 5-day median (42.1% vs. 45.1%; AOR, 0.90; 95% CI, 0.83–0.96) [43].

For a long time, a seven-day application of antibiotic therapy to treat infectious diseases was standard procedure [44]. However, the duration of antibiotic treatment should be based on the severity of the disease, patient characteristics, patients' clinical stability, and the causative organisms [45]. Long-term antibiotic treatment is associated with increased side- effects, antibiotic-resistant organisms, and *C. difficile* diarrhea [46, 47]. Unfortunately, a large study in 66,901 long-term care residents showed that 44.9% of patients were prescribed antibiotic treatment lasting longer than 7 days, and prescriptions tended not to be based on patient characteristics and comorbidities [14]. Furthermore, a retrospective cohort of 152,874 patients hospitalized for CAP found that more than 70% were prescribed antibiotics in excess of recommendations [48]. A large US study found that for 93% and 71% of patients with uncomplicated CAP and healthcare-associated pneumonia, respectively, lengthy durations of antibiotic treatment were indicated [49].

In addition, a systematic review of HAP in critically ill adults (including VAP) manifested that a short duration of antibiotic therapy (7 to 8 days) versus conventional antibiotic therapy (10 to 15 days) did not increase mortality rate, duration of mechanical ventilation, and length of hospital stay; however, a rise in recurrence was discovered in the subgroup of patients with VAP, caused by non-fermenting Gram-negative bacilli [50]. An RCT study in neonatal pneumonia conducted to compare the efficacy of a short course (4 days, intervention group) with a traditional antibiotic regimen (7 days, control group) demonstrated that treatment in the intervention group had the same success rate as in the control group, but the group intervention significantly reduced the length of the hospital stay, as well as antibiotic use and treatment costs [51].

For adults with CAP, although more relevant antibiotic studies are needed in the future to support a short-term therapy, clinicians should always be aware that the duration of antibiotic treatment should be based on the clinical improvement of the patient rather than mechanical practice. ATS/IDSA guidelines recommend a total duration of antibiotic therapy of 5 days for most outpatients and inpatients with CAP, except for cases of suspected *MRSA* or *P. aeruginosa*. According to the guidelines, the patient will achieve clinical improvement after the first 48–72 hours, after which antibiotics should be continued for 2–3 days [45]. Pending further studies, adherence to guidelines is one of the keys to limiting DRPs in treatment.

For pediatric patients with CAP, according to the 2011 PIDS/IDSA guidelines, which are still applicable today, the duration of treatment depends upon the severity. Treatment courses of 10 days are recommended, although the guidelines suggest that shorter courses may be just as effective, especially in mild patients. CA-MRSA patients may need a longer treatment period [26].

For adults with HAP/VAP, although the duration of antibiotic use is determined based on patients' conditions like a clinical improvement, as well as radiological and laboratory parameters, the current recommendation for most patients is a 7-day course of antimicrobial therapy rather than longer treatment [52].

In conclusion, the high rate of prolongation of antibiotic treatment and inappropriate initiation of therapy in patients with pneumonia indicates the great need for improvement to reduce drug-related problems. Antimicrobial stewardship, biomarkers, and clinical stability scores should be applied to decrease the duration of antibiotic therapy [53, 54].

2.4 Comorbidities

Respiratory diseases have been found to be associated with multi-morbidity patterns [55]. Patients with pneumonia often have a broad range of comorbid conditions [37, 56]. While short-term mortality is directly associated with the severity of pneumonia, long-term mortality is associated with comorbid conditions [56]. Most patients who die from pneumonia have one or more severe chronic diseases, such as cerebrovascular disease, chronic cardiac or renal disease, dementia, cachexia, mobility impairment, neoplastic metastatic disease, or sepsis. Patients with either MRSA or Pseudomonas were found to have an increased risk of dying of pneumonia [57]. In patients with pneumonia, comorbidities are also associated with poor response to treatment. Moreover, patients older than 80 years with comorbidities also have a higher mortality rate than patients from other age groups [58].

All-cause mortality has been found to increase in relation to the number of comorbid conditions. Every comorbid condition has been found to correlate with a 9% higher risk of death [56]. Some comorbid conditions that influence mortality (cardiovascular and lung diseases, diabetes, etc.) are also particular risk factors for pneumonia [37].

The Charlson Comorbidity Index measures comorbidity. Patients with a higher Charlson pathology index score were found to have a higher risk of death due to hospitalization (OR 1.28; 95% CI 1.07–1.53). These findings indicate a relationship between a patient's comorbid burden and the consequences of community-acquired pneumonia [59]. Results of a study among 108 patients by Franzen et al. indicated that the death risk of hospitalized pneumonia patients tended to increase with a higher CCI [58].

Children with comorbidities were more likely to be hospitalized for community-acquired pneumonia, compared to those without comorbidities. Approximately 50% of children and adolescents with community-acquired pneumonia had comorbidities related to malnutrition, as well as the use of antibiotics and hospitalization for community-acquired pneumonia during the previous 24 months. Bivariate analysis showed that patients with comorbidities demonstrated higher chances of malnutrition ($p = 0.002$), previous use of antibiotics ($p = 0.008$), and previous hospitalization for community-acquired pneumonia in the last 24 months ($p = 0.004$). In multivariate analysis, the following variables were independent predictors of community-acquired pneumonia in patients with comorbidities: malnutrition ($p = 0.008$; RR = 1.75; 95%CI 1.75–44.60); previous use of antibiotics ($p = 0.0013$; RR = 3.03; 95%CI 1.27–7.20); and previous hospitalization for community-acquired pneumonia ($p = 0.035$; RR = 2.91; 95%CI 1.08–7.90) [60].

In addition, pneumonia influenced concurrent comorbid conditions, resulting in a subsequent impact on the incidence of events like acute myocardial infarction, heart failure, stroke, venous thromboembolism, and cancer [56]. Recognition of the mutual relationship between pneumonia and comorbidities will help to identify patients at high risk. Though no specific guideline for multi-morbidities currently exists, close monitoring of patients during hospitalization and long-term follow-up may result in better outcomes.

2.5 Risk factors for DRP-readmission and pneumonia re-hospitalization

According to a review on drug-related hospital readmissions, an average of 21% of such readmissions were drug-related, and 69% were considered preventable [61]. Some predictive factors that can be considered to avoid hospital readmissions due to DRPs include limiting the number of drugs prescribed on a particular day, and the number of drug classifications according to the day of hospitalization [62]. Healthcare professionals should focus more on identifying risk factors related to drug-related readmissions, and on finding appropriate interventions.

Among the known risk factors for DRPs is non-adherence to medication, which may be aggravated by the complexity of the medication regimen. The medication regimen complexity index (MRCI) is a tool that assesses the complexity of a medication list in terms of dosage form, dosing frequency, and additional directions required for administration. Higher MRCI scores indicate greater regimen complexity. MRCI scores were significantly higher in patients readmitted (within 30 days) than those not readmitted [63, 64]. The MRCI can thus be used as a predictor of drug-related readmissions.

Another risk factor associated with 30-day readmission rates was the presence of comorbidities [65]. Comorbidities weaken the immune system and worsen a patient's condition. The Charlson Comorbidity Index (CCI) is a tool that adds weighted scores to each illness predictive of mortality. Some studies have reported a higher mean CCI in patients who were re-admitted [62, 65]. As the CCI apparently has a strong potential to be a readmission predictor, it has been recommended for inclusion in readmission prediction tools [63].

Risk factors for pneumonia re-hospitalization are currently among the most important problems to be dealt with. Possible risk factors for early re-hospitalizations include male gender, age ≥ 70 years, the longer length of stay during the first admission, and a Multisource Comorbidity Score (MCS) ≥ 10. As for therapy, for readmitted CAP patients whose underlying respiratory disease has not yet been determined, the value of inhaled therapy has not definitely been decided. "Inhaled steroids may favor CAP in COPD patients, whereas anticholinergics may favor CAP in asthma patients. It is difficult to differentiate the effect of inhaled therapy from the effect of COPD or asthma severity on the risk of CAP, and these relationships may not be causal, but could call attention to inhaled therapy in COPD and asthma patients." [66]. In pediatric patients infected with Mycoplasma pneumonia, readmission before 90 days after discharge is influenced by age, body temperature, and *influenza A* co-infection during hospitalization [67]. However, in adult patients, risk factors for readmission within 30 days after hospital discharge include the person's age, hospitalization frequency during 3 months, chronic respiratory failure, heart failure, chronic liver disease, and the (non)availability of home healthcare [68].

A post-discharge study was performed in which researchers phoned every patient within 48–96 hours after they left the hospital to ask about their medication adherence, any adverse drug events (ADEs), and their use of medication. The process of medication reconciliation identified 103 errors, or 2.4 errors per patient, especially errors related to inaccurate doses, frequency, or medications not included on the list of home medications (**Table 1**) [69].

Multivariable analysis showed pneumonia-related readmission to be connected to para/hemiplegia, malignancy, pneumonia severity index class ≥ 4, and clinical instability ≥ 1 upon hospital discharge. Comorbidities such as chronic lung disease and chronic kidney disease, treatment failure, and decompensation of comorbidities were correlated with the pneumonia-unrelated 30-day re-hospitalization rate [65].

Interventions (n = 186)	n (%)
Medication reconciliation (n = 103)	
Incorrect dose or frequency	49 (48)
Medication omitted	33 (32)
Medication added	14 (14)
Duplicate therapy	4 (4)
Counseled in nonadherence	3 (3)
Mean errors per patient[a]	2.4
Therapeutic recommendations (n = 38)	
Change route	29 (76)
Optimize therapy	7 (18)
De-escalate therapy	2 (5)
Discharge counseling (n = 45)	
Counseling on antibiotics[b]	33 (73)
Counseling on chronic medication changes	12 (27)

Note: All data are given as n (%) unless otherwise specified, and all percentages are rounded to the nearest whole number.
[a]*n = 43 patients.*
[b]*n = 39 patients were prescribed discharge antibiotics.*

Table 1.
Medication errors identified, and pharmacist interventions.

3. Strategies for reducing DRPs in pneumonia

3.1 Role of a clinical hospital pharmacist in patient care

Various interventions are needed, focused on reducing the risk of hospital readmissions by choosing transitional and territorial care and synchronizing post-discharge care [66]. Pharmacist-bundled interference was associated with a decline in the 30-day readmission rate for high-risk patients with pneumonia. Consequently, reducing hospital readmissions by supplying the greatest possible quality of health care is now becoming an essential consideration, also for the institutions themselves [69]. Also, identifying drug-resistant pathogens in pneumonia patients may help to determine the appropriate choice of empirical antibiotics. Further, building a model to define the patient's risk factors may help with the prescription of broad-spectrum antibiotics [70]. Antibiotic administration for outpatients can be improved by predicting factors related to inappropriate antibiotic regimens. Patients at risk of drug resistance are now among the predictors of unsuitable antibiotic regimens [21].

The outcomes of this pilot research show that a pharmacist-specific bundled intervention, involving medication reconciliation, curative advice, patient discharge direction, and a research phone call, was associated with a decreased 30-day readmission rate for high-risk patients with pneumonia. The more than 200 total interventions reported suggest countless promising opportunities for increased pharmacist participation in care. Permitting pharmacists to devote time and effort to high-risk patient populations could confirm their value in supporting and expanding services to other people in the future, as well as reduce health care prices, and eventually the extent of welfare patient care [69].

Modifying the route of administration (ex- or intravenous to oral) was the most popular intervention, second to optimizing therapy. Optimizing therapy included making suitable renal doses and suggesting substitute regimens, especially if a patient's inpatient antibiotic regimen was the same as an outpatient regimen that had failed, or if he or she had risk factors for a healthcare-associated infection. Regarding the element of discharge counseling in the intervention, 91% of patients chosen prospectively for a pilot study received such counseling. This single-center pilot research concentrated on the influence pharmacists can have on transitions of care and readmission rates, using interventions like medication reconciliation, therapeutic recommendations, discharge instructions, and follow-up [66].

3.2 Antibiotic stewardship programs

J.E. McGowan Jr. and D.N. Gerding were the first to create the term "antimicrobial stewardship" in an article published in 1996. They wanted to emphasize the need for appropriate antibiotic prescription in order to prevent resistance [71]. IDSA defined these as "antibiotic stewardship programs referring to coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents" [72]. The 5 "Rs" of anti-microbial stewardship are: "the right drug at the right time with the right dose for the right bug for the right duration" [16]. The goals of ASP increase treatment effectiveness while reducing *C. difficile* infections, adverse effects, antibiotic resistance, hospital costs, and lengths of stay. Some activities related to antibiotic stewardship in CAP include monitoring the de-escalation and duration of antibiotic treatment, complying with treatment guidelines, switching from intravenous to oral antibiotic treatments, prospective auditing, and developing the multidisciplinary team [73]. Antibiotic stewardship contributes to rational prescription of antibiotics, increases treatment effectiveness, and reduces side-effects and antibiotic resistance. A multi-center, pre-empirical, quasi-experimental study including 600 CAP patients (307 in the historical control group and 293 in the stewardship intervention group) showed that antibiotic stewardship helped to increase guideline-concordance to the duration of antibiotic therapy from 5.6% in the historical group to 42% in the intervention group ($P = 0.001$). The intervention group received a significantly shorter mean duration of treatment than the historical group (6 (5–7) versus 9 (7–10) days, $P = 0.001$). Antibiotic stewardship helped to avoid a total of 586 days of unnecessary antibiotics during the 6-month intervention period, while incidence of readmission for CAP, mortality rate within 30 days post-discharge were similar in both groups [54]. A multicenter randomized trial including 312 hospitalized CAP patients found that the duration of antibiotic therapy as determined by the physician (control group) was longer than in the guideline-concordant group (intervention group): (median, 10 days [interquartile range, 10–11]) versus 5 days (interquartile range, 5–6.5), respectively; $P < .001$). Clinical success was similar between both groups, at both 10 days (48.6% versus 56.3%) and 30 days (88.6% versus 91.9%) after admission [73].

The major activities and elements of ASPs include [74]:

- Hospital Leadership Commitment
- Accountability
- Pharmacy Expertise
- Action

- Tracking
- Reporting
- Education

Hospital Leadership Commitment: The senior leadership of the hospital, especially the chief medical officer, plays an important role in the success of ASPs. Hospital leadership helps to provide ASPs with the resources needed to achieve their goals.

Accountability: ASPs must have a designated leader or co-leaders, such as a physician and pharmacist, who have effective leadership, management, and communication skills, and are responsible for program management and outcomes.

Pharmacy Expertise: The participation of pharmacists, ideally as co-leaders of ASPs, will help to make ASPs highly effective. In large hospitals, pharmacists with infectious disease training are designated, but in hospitals without infectious disease trained pharmacists, general clinical pharmacists are appointed to help lead implementation efforts to improve antibiotic use.

Action: Antibiotic stewardship interventions are initiated to improve antibiotic use. Some activities related to antibiotic stewardship in CAP include prospective audit and feedback, such as monitoring the de-escalation and duration of antibiotic treatment, complying with treatment guidelines, switching from intravenous to oral antibiotic treatments, and preauthorization. The three priority interventions are: prospective audit and feedback, preauthorization, and facility-specific treatment guidelines.

- Preauthorization: This requires prescribers to gain approval prior to the use of certain antibiotics. This can help to optimize initial empiric therapy. The development of preauthorization for necessary antibiotics can be based on standard guidelines; limited antibiotics can be prescribed based on consultation, or more easily, referring to the WHO antibiotic classification. In 2017, WHO proposed categorizing antibiotics into three groups: ACCESS, WATCH, and RESERVE groups [75]. For the WATCH group, antibiotics with a high risk of resistance, such as 3rd-generation cephalosporins, carbapenems, and fluoroquinolones, should be preauthorized; for the RESERVE group, antibiotics such as colistin, ceftaroline, tigecycline, and aztreonam are indicated when other prescribed antibiotics have failed or are inadequate (e.g., serious life-threatening infections due to multidrug-resistant bacteria), and must be authorized and discussed before prescribing.

- Prospective audit and feedback: This is an external assessment of antibiotic therapy by ASP experts at some point after the agent has been prescribed. The ASP prospective audit and feedback team usually consists of a physician (an infectious disease specialist or a clinical microbiologist) and a clinical pharmacist. Prospective audit and feedback are performed as follows: On the first day of prescribed antibiotics, the team audits the suitability of doses and the routes of empirical antibiotic therapy. After 72 hours, the team reviews the patient's response (clinical stability, biomarkers, renal function), along with microbiological culture results, to give feedback to the treating physician in case a need to change the therapy is indicated: change of antibiotic, the addition of antibiotic, de-escalation of antibiotic treatment, dose adjustment. The cycle of audit and feedback is performed continuously. On day 7, the team evaluates the duration of antibiotic treatment (**Figure 1**) [76]. Preauthorization and

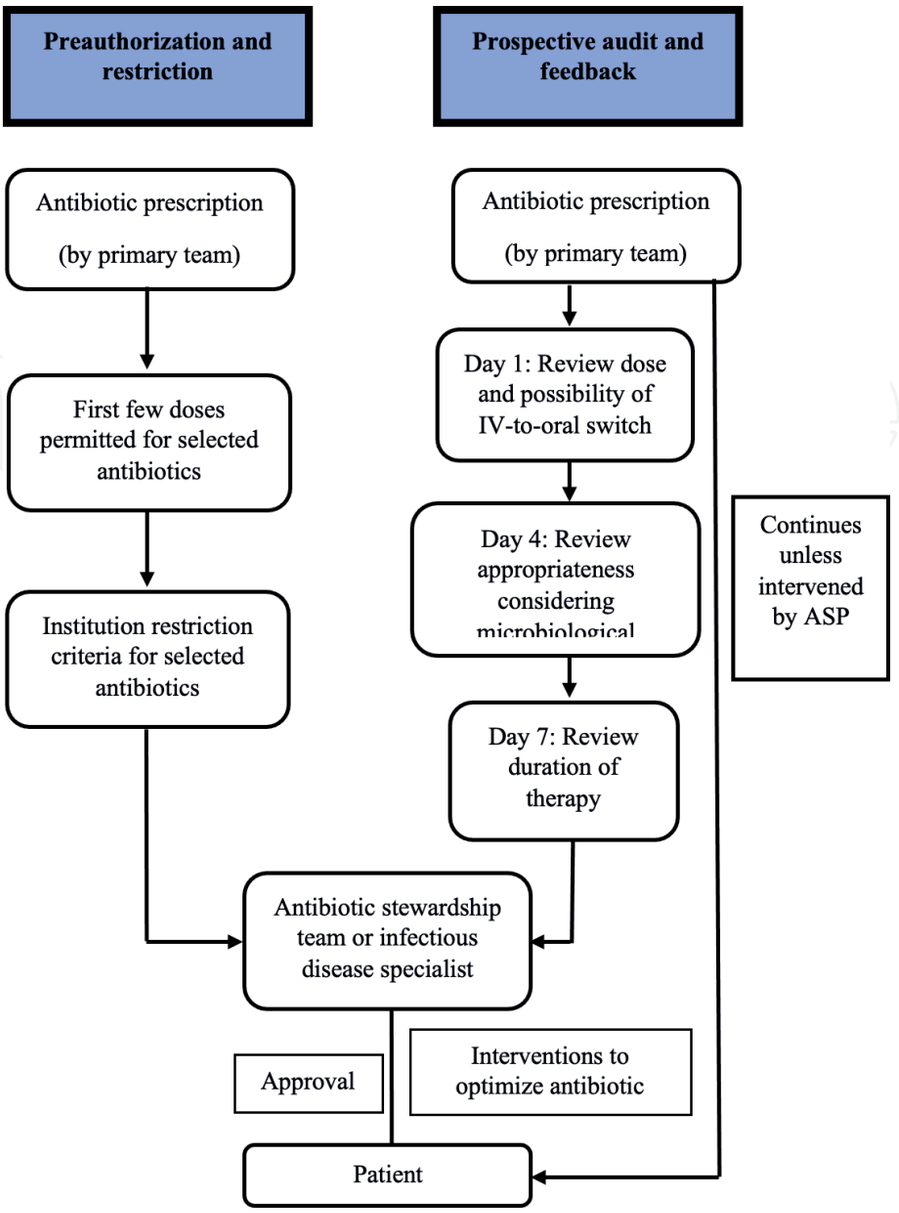

Figure 1.
Schema for prospective audit and feedback, and formulary restriction and preauthorization, for ASPs.

prospective audit and feedback are complementary processes that optimize antibiotic therapy. Preauthorization resembles an antibiotic input "filter" that improves initiation of antibiotics, and prospective audit and feedback help to optimize continued therapy.

- Facility-specific treatment guidelines: A clear guideline on antibiotic use will help to make prospective audit and feedback easier and more effective. Recommendations should be developed based on national and international guidelines, local susceptibilities, and hospital antibiotic management policies.

Tracking: Measurement is crucial to identify opportunities for improvement and to assess the impact of interventions. Measurement of antibiotic stewardship interventions may include measures of antibiotic use, and measures of outcomes like *C. difficile* infections, antibiotic resistance, and financial impact.

Reporting: A comprehensive picture of antibiotic use and antibiotic resistance, along with the work of the antibiotic stewardship program, should be provided in regular updates to prescribers, pharmacists, nurses, and leadership. This helps make

medical staff aware of the situation of antibiotic use and antibiotic resistance at their facility, thereby promoting rational use of antibiotics.

Education: Interventions (preauthorization, prospective audit, and feedback) and measurement of antibiotic use and outcomes, can reveal gaps in antibiotic prescribing in hospitals. This helps to make the education of medical professionals realistic and effective, thereby gradually improving the effectiveness of antibiotic treatment, reducing adverse effects, antibiotic resistance, and treatment costs. There are many ways to provide education regarding antibiotic use, such as presentations; posters, flyers, and newsletters; and/or electronic communication to staff groups.

In summary, ASP interventions applied in hospitals, such as audit and feedback, updating of treatment guidelines along with local susceptibility patterns, and training of medical staff, can reveal individual or departmental cases of high antibiotic use by infectious disease specialists, clinical pharmacists, and microbiologists in order to promote rational antibiotic use [77].

3.3 Technological tools

3.3.1 Biomarkers

Among the oldest and most frequently used biomarkers for predicting a patient's response to antibiotic therapy are fever and leukocytosis. A decline in both indicates that an infectious disease has been adequately treated with a chosen course of antibiotics. More recently, studies have shown that another biomarker, procalcitonin (PCT), can be combined with clinical criteria to help physicians to decide whether to de-escalate or discontinue antibiotic therapy, without affecting outcomes [78]. A systematic review of 26 RCTs involving 6708 participants (acute respiratory infections) from 12 countries found that the duration of antibiotic therapy using PCT concentration reduced mortality, decreased antibiotic consumption, and lowered the risk of antibiotic side-effects. The length of hospital stay and ICU stay were similar in both groups [79]. A randomized trial of 621 patients with suspected community or hospital infection showed that the intervention group (using PCT) had a significantly shorter duration of antibiotic treatment than the control group (14.3 days (SD 9.1) vs. 11.6 days (SD 8.2); absolute difference 2.7 days, 95% CI 1.4 to 4.1, $p < 0.0001$) [80]. Similarly, an RCT of 101 patients with VAP indicated that antibiotic discontinuation based on serum PCT decreased their duration of antibiotic use compared with the control group ($p = 0.038$) [81]. A novel multicenter quality control survey study, including 1759 patients from Switzerland, France, and the United States who had respiratory tract infections, revealed that antibiotic therapy duration based on PCT concentration was shorter than without PCT concentration (5.9 vs. 7.4 days; the absolute difference in days (95% CI), −1.51 (−2.04 to −0.98); $P < 0.001$) [82]. The Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) suggest using PCT levels plus clinical criteria, rather than clinical criteria alone (weak recommendation, low-quality evidence), to guide discontinuation of antibiotic therapy [52].

Besides PCT, another biomarker useful in the management of pneumonia is C-reactive protein (CRP). Together with clinical criteria, low levels of CRP and PCT at 72 h of CAP treatment may improve the prognosis of an absence of severe complications [83]. In a study by Shuren Guo et al., performed on 350 hospitalized CAP patients, CRT and PCT levels on day 3 were statistically lower in the survivors compared to non-survivors [84]. The European Respiratory Society recommended that for patients with suspected pneumonia, along with observing clinical signs and

symptoms, a CRP test may be indicated. A CRP level of >100 mg/L, with symptoms for >24 hours makes pneumonia likely; a CRP level < 20 mg/L at presentation, with symptoms for >24 hours, is possibly caused by another respiratory tract infection [85].

Antibiotic resistance is one of the greatest threats to global health, and pneumonia is one of several infections that are becoming less responsive to antibiotic treatment. Antibiotic resistance increases the risk of mortality, prolongs hospital stays, and increases treatment costs. The unnecessary and prolonged use of antibiotics is an important cause contributing to the growth of multidrug-resistant bacteria [86]. This "one size fits all" approach can result in overtreatment, increased side effects, and antibiotic resistance. Therefore, individualization in treatment is important. In addition to clinical assessment, the physician may further consider assessing serum PCT and CRP levels to guide clinical decision-making.

3.3.2 Computerized provider order entry (CPOE) and clinical decision support system (CDSS)

Two useful tools which help in the prevention of ADEs are the computerized physician order entry (CPOE) and clinical decision support systems (CDSS). Compared with conventional medication control, the computerized alert system ADEAS selected different patients based on the risk of an ADE. For the hospital pharmacist, this makes ADEAS a valuable and appropriate tool in reducing the number of preventable ADEs [87].

The implementation of CPOE and advanced CDSS tools substantially increases the number of possible ADE alerts for pharmacist review, and the number of true-positive ADE alerts per 1000 admissions [88].

In a statistical study involving 592 patients during the paper-based prescribing period and 603 patients in the CPOE/CDSS period, the total cost of the paper-based system was €12.37 per patient/day, and of CPOE/CDSS was €14.91 per patient/day. Incremental Cost-Effectiveness Ratios (ICER) for medication errors and for preventable adverse drug events were 3.54 and 322.70, respectively; this indicates the additional amount (€) necessary to prevent a medication error or an ADE. CPOE with primary CDSS contributes to the reduction of the risk of preventable harm. Overall, the additional CPOE/CDSS costs required to prevent medication errors or ADEs appear to be acceptable [89].

However, another study indicated a need to optimize the sensitivity of CPOE/CDSS to detect certain classes of problems, because most DRPs identified by clinical pharmacists were not detected in daily clinical practice by CPOE/CDSS. This underlines the importance of the clinical pharmacist's involvement to reduce DRPs [90].

4. Conclusion

Pneumonia is one of the respiratory diseases causing the highest mortality rate in children and the elderly. As the elderly often have many comorbidities, DRPs also greatly affect their condition and ability to recover.

DRPs in pneumonia are a very complex issue, requiring great attention from healthcare professionals and patients in prescribing, dispensing, and administering medications. Moreover, the rate of hospital readmissions for pneumonia is also a challenging burden, for the health system in general and for patients in particular. The application of technological tools such as CPOE and CDSS to prescribing and ordering can reduce the occurrence of DRPs, but it is physicians, clinical pharmacists and health professionals who play the most important role in reducing DRPs and hospital readmissions in pneumonia.

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