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A Review on the Clinical Guidelines to Pediatric Pneumonia and Assessment of the Extent to which these Guidelines are Followed in Pakistan

Abstract *Pneumonia is a respiratory disease that can be life-threatening when worsened or not treated properly. There are various standard guidelines, including WHO guidelines for the management of Pneumonia, for both children and adults as well as for the geriatric patients, based upon individualized therapy to each patient. These guidelines ensure the rational use of medications so as to target and achieve definite patient outcomes. Further reading will take towards such standard guidelines specifically for the management of paediatric Pneumonia and will assess the extent to which the stated guidelines are followed in different areas of Pakistan. Moreover, this review article will also emphasize the gaps that lead to irrational use of the medications in Pakistan and will highlight the strategies and plans that can be adopted at community and national levels to implement rational drug use for direct patient care and definite patient outcomes.*

Key Words: Pneumonia, Paediatric, Disease, Pakistan, Guidelines

Introduction

Pneumonia is characterized as inflammation and infection of the lungs that demand antibiotics. During the infection, lungs get filled with the pus of fluid that causes difficulty in breathing. It can't render it's soul occurrence to a single pathogen because it has different causes. It is classified according to it's cause, or it's a location that inflicts Pneumonia on the patient. It should be treated immediately; otherwise, the condition may worsen. There is a chance that the infection may spread to other body parts (Fabrigas et al, 1999). Children fell easy prey to this infectious disease (paediatric Pneumonia) which is resolved by health experts following various standard guidelines. A child may receive it outside the hospital vicinity and other health care facilities (community-acquired Pneumonia - CAP). Viral causes include influenza virus and human rhinovirus, whereas bacterial causes include Streptococcus pneumoniae, Staphylococcus aureas, and Enterobacteriaceae. Some other bacterias which cause CAP include Mycoplasma pneumonia, Chlamydophilla pneumonia, Haemophilus influenzae, Mycobacterium Tuberculosis, Legionella, and Pseudomonas aeruginosa.

Community-Acquired Pneumonia also affects children. The symptoms include cough, tachypnea, retractions, abdominal pain, hypoxemia, lethargy and grunting. Whenever a patient is examined physically, he shows crackles, decreases breathe sounds, rales, and wheezing when lung fields are auscultated with the help of stethoscope.

Whatever the cause of Pneumonia may be, proper history, physical examination, and awareness of the cause are always required. This article gives us an overview of the guidelines that are being followed in Pakistan and the extent to which they are applicable or being applied for the management of paediatric Pneumonia. Different trials are conducted to test the already existing standard treatments

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to bring changes in them. In Pakistan, guidelines of the World Health Organization (WHO) are being implemented mostly. Physicians go for any treatment after considering the signs and symptoms appearing in a patient.

Guidelines for Treating Community-Acquired Pneumonia

Patients are managed even outside the hospitals (outpatients). Nowadays, Severity Assessment Tools help doctors to individualize the treatment for the patient. The individuals who are eligible candidates for outpatient treatment, their first-line treatment is through azithromycin, which is a macrolide. Azithromycin targets Streptococcus pneumonia. An alternative option, in this case, is Doxycycline (Sialer et al, 2013)

CAP in children is identified by the absence of tachypnea. Patient's age, the severity of illness and the resisting patterns of pathogens are considered in children to choose an antibiotic. The children suffering from non-severe CAP, yet hospitalized, are given amoxicillin orally or penicillin-G intravenously. The children from five to sixteen years are given macrolides as empiric antibiotics.

If children are vaccinated with pneumococcal vaccine, it would eventually reduce the chances of occurrence of Pneumonia.

Non-Resolving Pneumonia

If two or three episodes of Pneumonia occur in a person during one year, it can be called non-resolving Pneumonia. Newly born and other children often become a victim to this. If symptoms persist along with roentgenographic abnormalities for more than a month, it is considered non-resolving Pneumonia. The treating antibiotics fail to show adequate response. There is a **6-15%** chance for the treatment to fail, which would result in mortality. This kind of Pneumonia deteriorates into two variations. The first one is progressive Pneumonia which is characterized by clinical fluctuations, and secondly, persistent Pneumonia with no clinical stability. When this kind of Pneumonia progresses, it leads to septic shock and respiratory failure.

For the treatment, go for microbiology tests and repeated blood cultures. However, urine testing can also be performed. Chest CT is performed to see the progress of treatment as it would clearly show lung abscesses and pleural effusions or pulmonary embolism. (Cook DJ et al., 1998)

Ventilator-Associated Pneumonia (VAP)

It is based on a technological machine that is made in terms of Pneumonia, in which patients get ventilated for a minimum of 24 hours to a maximum of 48 hours through tracheostomy mediums. (Amanullah et al., 2015) The mechanical models of the ventilators tend to modify the tracheostomy and, or pharyngeal systems and surroundings to allow the gastric and oral to be an entrant in the lower airways, which reduce the bacterial infection to spread at the beginning of the ventilator processes. (Cook DJ et al., 1998)

Diagnostic Criteria

The VAP machines are suggested to detect pulmonary infections like flu, fever and other minor infections that seem to accept the bacterial interference in the processes of the ventilator. The criteria for diagnostic were recorded 65% as minimum, and 75% as a higher percentage (Fabregas et al, 1999). Other criteria for the diagnostic machineries would be the detection of several minor diseases and radiologic and laboratory criteria. (Horan et al, 1659) Whenever the VAP is exactly suspected in any patient, the patients are likely to prefer quick treatment. If the patient did not get diagnosed quickly, it would lead to high morbidity and mortality with the microbial culprit (El kuti et al 2008)(Swanson et al, 2013)

Diagnostic Testing

A sampling which secretion in nature is required for the bacterial testing and confirmation through a bronchoscope and non-bronchoscope methods and mediums. An ultra and higher sound leading instructions are suggested to get the pleural fluid when found. Some particles from the endotracheal can be found quickly, but it impact as high airways in the ICU systems for the patients who have a high false-positive rate. For the bronchoscope processes, expert bronchoscopes are required, which will have a command over the distal airways and over the protected specimen brush technologies (Amanullah et al, 2015).

Antibiotic Treatment

If a patient is facing any risk of multi-drug resistant (MDR) pathogens, then the antibiotic treatment is selected on the basis of the patient condition on being early or late VPA processes (Figure 1). The treatment is simply designed to treat a patient with a specific percentage of the bacteria which requires information about the local distribution of the pathogens (Beadsley et al., 2006). Doses and frequency of the treatment of the antibiotics are specifically mentioned according to the patient's type. Many of the antibiotic choices are made on the basis of the antimicrobial agents, which are resistance warrants. The consultation of the antibiotics for any physical and biological disease would be preferred to take from any of the expert pharmacists (role of pharmacist intervention).

Following antibiotics are preferred to treat the early stage of CAP

- Ceftriaxone.
- Fluroquinolone.
- Ampicillin- Sulbactam combination.
- Ertapenem.

Table 1. Showing ventilator associated Pneumonia related MDR risk factors. (MDR - multi-drug resistant).

VAP Related Multi-Drug Resistant Risk Factors		
Risk factors of MDR Pathogens	**Risk factors of MDR Pneumonia and other Gram–Bacilli**	**Risk Factors Related to Methicillin-Resistant Staphylococcus Aureus (MRSA)**
- If intravenous antibiotics are used within the previous 4 months. - Distress syndrome in adults before VAP. - Non-empirical treatment of VAP (more than 5 days in ICU). - VAP immediately after dialysis.	Treatment of a patient being in an ICU: 1. >10grams negative isolates are being treated with 1 or more antibiotics referred used by VAP. 2. Unknown susceptibilities in local antimicrobial are unknown.	Treatment on setting in a medical ward/ICU: 1. Infections from MRSA are less then **10-20%.**

Pediatric Pneumonia

About 13% of toddlers and infants suffer from this severe illness, and it can be the cause of death mostly in children up to 5 years old, and almost 15% of deaths in children are recorded every year because of this disease. This kind of Pneumonia could be age-specific or pathogen-specific. Streptococci, Klebsiella, Escherichiacoli and Listeriamonocytogenes are present in the birth canal, so the neonates are at risk of catching infection by any one of these organisms. Streptococcus pneumoniae, Streptococcus pyrogen and Staphylococcus aureus may also be the causative agent but they are identified later. The child till age of 2 gets Pneumonia through viruses mainly. Cases related to S.pneumoniae and H.influenzae type B infect children with age up to 5 years. Then comes the upper years that are till age 13. Here Mycoplasma pneumonia and Streptococcus pneumonia are responsible. (CookDJ et, 1998) Treatment begins after physically examining and identifying the causative agent. Supportive treatment is given through antipyretics, fluids for hydration, and oxygen for hypoxia. Antibiotics aren't given in viral Pneumonia and non-infectious Pneumonia, so here, this supportive treatment is carried out. For bacterial Pneumonia, neonates are given ampicillin and an aminoglycoside. They can also be given a cephalosporin from the third generation. Do not give ceftriaxone because it might lead to kernicterus. (CookDJ et al., 1998)

Children with ages of 1-3 years are prone to atypical Pneumonia, which is treated through erythromycin or clarithromycin. Infants older than 3 months are given amoxicillin orally. However, another beta-lactam antibiotics can be given. For children older than 5 years, macrolides are considered first-line therapy. Special focus for children should be in sight who have other illnesses prevailing side wise:

- Children with sickle cell anemia need cefotaxime, macrolide or vancomycin.
- Children with cystic fibrosis will be given penicillin or ceftazidime along with vibramycin.
- For varicella, use acyclovir.
- For the respiratory syncytial virus (RSV), use ribavirin with patients at higher risks.
- Patients with HIV are treated with sulfamethoxazole/trimethoprim and prednisone.
- For cytomegalovirus, ganciclovir and gamma globulin are the preferred ones.
- MRSA (suspected), use clindamycin or vancomycin.

Diagnosis

Childhood pneumonia (CP) indicates most of the signs and symptoms which are non-specific or commonly depends upon the nature of the patient, like the demographics, health background and history and other biological terms. The most common, also universal symptom of CP, is a cough which is a base symptom for CP patients. Later the patient identifies many signs and symptoms like headache, chest pain, arthralgia and nausea. (Stuckey et al. 2012) .The most accurate signs to recognize CP include fever, low heartbeat, difficulty in breathing. Many other physical body symptoms appear at the beginning stages. (Margolis et al. 1998). The diagnostic testing and sampling processes require some criteria based on testing, which includes the oxygen saturation test, the heart radiography through the chest, whole blood cell count, PCR test and ultrasound. (Neuman et al, 2017). The blood culture remains non-valid and valid in the literature, but many of the recent researches depict that it isn't sensitive for pneumonia diseases in children, while the American hospitals made use of blood culture testing mandatory in paediatric patients with Pneumonia (Bradley et al, 2011).

Outpatient Vs Inpatient

To treat the children correctly and properly who is suffering from Pneumonia, the identification of the severity of the Pneumonia is required along with the clinical status of the child. Most of the children don't require inpatient treatments because the treatment must be empirical in form, and the child gets to the hospital quickly. (Table 2)

Antibiotic Treatment Guidelines

As discussed above, CP needs to be treated with a quick and empirical process, and for these processes, the demographics, the biological and health history of the patient is required for the correct treatment, which can be specifically designed for a specific patient. Outpatient treatments are mostly done on toddlers and children with pneumonia illness with oral antibiotics. The first priority is always to give a dose of amoxicillin; in case it's not available, then the preferred alternatives, cephalosporin and

macrolide antibiotics, are used to treat this illness (Neuman et al., 2007). (Table 3) Then comes a specific case of MDR pathogens, in which quinolones are preferred for empirical use.

Table 2. Showing criteria for Pneumonia in children as Regards Empirical Hospitalization.

Criteria's for Pneumonia in children who Require Empirical Hospitalization
CAP infections mostly found in infants of 3 to 6 months old.
Temperature reaches 39C (102 F).
Infants and children who have respiratory distress with 92% of oxygen saturation.
Infants and children who have heart or asthma diseases are most likely to acquire Pneumonia.
Poor feeding and dehydration in infants and children.

In children, the quinolones are preferred because it helps children organisms to develop without any disability side effect.

Table 3. Showing WHO Guidelines as regards outpatient Paediatric Pneumonia Treatment.

WHO Guidelines for Outpatient Pneumonia Paediatric Treatment		
Age	**Preferred treatment**	**Alternatives**
0-5 years old		
Viral	No required treatment.	Antiviral against influenza.
Bacterial	Amoxicillin	Third generation cephalosporin and amoxicillin-clavulanate.
Age (5-16) years old		
Viral	No treatment is required.	Antiviral against influenza.
Bacterial	Amoxicillin	3rd generation or amoxicillin-clavulanate
Atypical bacteria	Oxycycline or Macrolide.	If older than 8 years, quinolones are alternatives.

For in-patients, treatment guidelines are given in Table 4. For outpatient treatment, average time of the whole treatment falls between 5 to 10 days (Stuckey et al., 2012), while the inpatient treatment takes a long time because of the antibiotic therapies including parental and oral therapies.

Table 4. Showing WHO guidelines as regards Inpatient Paediatric Pneumonia Treatment.

WHO Instruction for the Inpatient Children Pneumonia Antibiotics		
Age	**Ideal**	**Alternative**
0-6 months old		
Bacterial	Derivative of IV penicillin along with cephalosporin (3rd generation).	Aminoglycoside ; macrolide in case of uncertain atypical organism
6 months to 5 year		
Bacterial	Ampicillin associated with IV derivative of penicillin.	Third-generation cephalosporin.
MRSA	Clindamycin or Vancomycin along with beta-lactam antibiotic.	Beta-lactam antibiotic along with clindamycin or vancomycin.
Infection caused by atypical bacteria	Macrolide	Beta lactam accompanied with macrolide.
5 to 16 years		
Bacterial	Derivative of IV penicillin associated with ampicillin.	3rd generation cephalosporin .
MRSA	Beta-lactam antibiotic along with vancomycin and clindamycin	Vancomycin or clindamycin (along with beta-lactam antibiotic)
Atypical bacterial infection	Macrolide.	Macrolide (along with beta-lactam antibiotic)
Caustic Pneumonia or ICU admitted.	Third-generation of cephalosporin, along with macrolide or vancomycin.	Doxycycline or vancomycin in addition to 3rd generation cephalosporin, along with nafcillin + antiviral + macrolide as optional.

Assessment of Following Standard Guidelines for Management of Paediatric Pneumonia In Pakistan with or Under Age 9

In order to evaluate the prescribing trends and errors that occur in the most frequently prescribed antibiotics in children (who are suffering from an acute infection of the respiratory tract and have different lengths of stay in a

hospital), a cross-sectional retrospective study was conducted in five tertiary care public hospitals of Lahore in 2017 from 1st January to 30th June. The age of the study participants was up to 9 years. The data of about twelve thousand patients were collected out of which about eighty percent of paediatric patients were suffering from acute infection of the lower respiratory tract and have long length of stay in hospital. The most frequently prescribed antibiotic was penicillin (fifty-two percent), followed by cephalosporin (sixteen percent) and then macrolides (nine percent). Approximately forty percent of the patients have errors in their antibiotic prescriptions. Twenty percent had errors related to the wrong dose, nineteen percent had errors related to wrong frequency, and eighteen percent had duplicate therapy errors. Mostly these errors were recorded in those patients who have long length of stay in hospitals. (Saleem, Z. et al.,2019)

Age of 2 Months to 4 Years

A study was conducted in Karachi among low income people. The age of study participants was two to fifty nine months. The study participants met the WHO criteria for non severe Pneumonia. They were assigned randomly a three day course of amoxicillin suspension of fifty mg per ml or matched volume of placebo i.e. test regimen according to the weight bands of WHO (five hundred mg every twelve hours for a weight of four to nine kg, thousand mg every twelve hours for a weight of ten to thirteen kg, and fifteen hundred mg every twelve hours for a weight of fourteen to twenty kg), but the result of this three day course of amoxicillin or placebo was yet a treatment failure. So we concluded that for children less than five years of age, treatment failure frequency was more in the placebo group than in the amoxicillin treated group.

Under Age 5

As Pneumonia is the leading cause of death among Pakistani children for less than five years of age and living in the Himalayan region. So a study was conducted in these high altitude regions of Pakistan in order to determine the incidence of severe Pneumonia among these children. In order to conduct this study health centre staff of 15 health facilities in punial and Ishkoman used integrated management of childhood illness criteria to identify the sick children under the age of thirty five months who have cough, difficulty in breathing, fast breathing and chest in drawing. Approximately five thousand children were enrolled for a period of fourteen months, out of which they identified fourteen hundred cases of Pneumonia and four hundred cases of severe Pneumonia. So the conclusion was that the incidence of Pneumonia is greater in children living at higher altitude than those living at low altitude. (Amir J Khan et al, 2009)

Age of 2 to 10 Years

A study was conducted in Nishtar hospital of Multan to determine the frequency of anaemia in hospitalized children who were suffering from Pneumonia. The study participants include 145 children out of which 75 were boys and 70 were girls whom history regarding fever, cough and tachypnea was taken and all the baseline investigations regarding the chest X-ray and blood test were done. Their age limit was 2 to 10 years. The mean haemoglobin level was noted to be 9.70 g/dl. The minimum hb level was 6.5g/dl, while the maximum hb level was 12.6 g/dl. In ninety-one percent of the study cases, anaemia was present. Anaemia is associated with female gender, mothers educational level and poor social status. Most of our paediatricians do not consider anaemia while treating Pneumonia so they must check haemoglobin levels on a routine basis in paediatrics suffering from Pneumonia. (Dr. Nazish Rani et al, 2018)

Risk Factors for Childhood Pneumonia

A study was conducted in north eastern Pakistan to determine the risk factors for the childhood pneumonia. This study was conducted in the children hospital and institute of child health Lahore. Total **180** cases of Pneumonia were studied, out of which **100** were complicated cases, and 80 were uncomplicated. In both these groups, history was taken in detail. Mean, and standard deviation was used to analyze the quantitative risk factors like child age, maternal and father age. Chi square test and finding odd ratios were used to analyze the qualitative risk factors like method of feeding, anaemia, immunization and non vaccination. From results of this study, it is to be concluded that anaemia, bottle feeding, non vaccination, malnutrition and rickets are the major risk factors for the complicated Pneumonia. (Sommaya Aftab et al, 2017)

Comparison of Co-Trimoxazole Efficacy with Amoxicillin

In order to compare the efficacy of co-trimoxazole with amoxicillin twice daily for the treatment of Pneumonia, a randomized controlled clinical trial was carried out in seven hospitals of Pakistan and in one community health service. About fourteen hundred and seventy one children with non severe Pneumonia under the age of fifty nine months were recruited for the study. 730 study participants were randomly assigned twenty-five mg of amoxicillin per kg of their body weight, and 741 participants were randomly assigned four mg per kg trimethoprim plus twenty mg per kg sulphamethoxazole. Both of these drugs were given for five days twice daily by oral route. The results showed that in the amoxicillin treated patients, the failure rate was 16.1%, and it was 18.9% in co-trimoxazole treated patients. Further analysis showed that the chances of treatment failure are more in children who had a history of breathing difficulty and who are ill for more than three days before coming to the hospital. So it is to be concluded that both the amoxicillin and co-trimoxazole have equal efficacy in treating non-severe Pneumonia, and to prevent the further worsening of disease, good follow up is an essential part. (Dr. tabish hazir et al,2002)

Chest X-Ray in Children (2 - 59 Months)

According to IMNCI guidelines, chest x-ray has been a promising diagnostic technique for Pneumonia. To determine this, a study was performed in Hyderabad and included suspected children with ages ranging from two to fifty-nine months. The study subjects were being undergone chest x-ray analysis for the diagnosis of Pneumonia. On concluding the study, it was found that about more than 60% of the study subjects had consolidations found on performing chest x-ray and about more than 65% of the study subjects had reticular shadowing in their respective chest x-rays. So, it was concluded that chest x-ray is sensitive enough to diagnose Pneumonia appropriately. (Jiskani, F. B. et al, 2017).

Lower Respiratory Tract Infection under Age 5

In about seven health care facilities of Punjab, a retrospective study upon hospitalized patients with or under 5 years of age with lower respiratory tract infection (LRTI) [including community acquired Pneumonia (CAP)] was assessed for appropriateness for the use of antibiotics (British National Formulary guidelines) for LRTI (Zia ul Mustafa et al., 2021). This study demonstrated alarming irrational use of the medications in children in terms of;

- Use of the drugs having the same therapeutic effect (synergistic effect/overuse of antibiotics) leading to adverse events in children.
- Use of multiple antibiotics of different classes indicating polypharmacy and also the lack of proper diagnosis by the physician.
- Wrong dose administered.
- Administered via wrong route.

With or Under Age 12

In about six health care facilities of Punjab, a retrospective cross-sectional study upon patients with or under 12 years of age with upper respiratory tract infection (URTI) was reviewed for appropriateness for the use of medications including;

- Cephalosporins,
- Penicillins and
- Injectable antibiotics

These medications were indicated as per British National Formulary guidelines and were also laid down by WHO in its prescribing indicatos for URTI (Zia ul Mustafa et al, 2020). This study demonstrated alarming irrational use of such medications in children diseased with Pneumonia as discussed above.

Assessing Cause of Pneumonia in Children (1-5 Years)

In Peshawar Pakistan, a cross-sectional study was held, in children aged 1-5 years. This was then analyzed for the possible cause of Pneumonia by culture techniques (assessing the diagnosis of Pneumonia). It was found that for children aged 1-2 years, Staphylococcus aureus and Staphylococcus pneumoniae were the main responsible microbes for Pneumonia, followed by Hemophilus influenza. And for children aged above 2 years, all the causative microbes were the same in all the age groups. (Farman Ali et al.,2019)

Fast Breathing Pneumonia in Children (2-59 Months)

As cotrimoxazole and amoxicillin (WHO recommended) both are in use for the treatment of fast breathing pneumonia in children, a study in Haripur district, Pakistan, was conducted, which was unblinded randomized trial in nature. It included children with fast breathing pneumonia, with ages ranging from two to fifty-nine months. The study participants were given treatment with two different regimens.

1. Amoxicillin suspension (oral) - 50mg per kg per day (to be continued for 3 days).
2. Co trimoxazole suspension - 8mg trimethoprim per kg and 40mg sulfamethoxazole per kg per day (to be continued for 5 days).

On concluding the study, the outcome was in favour of 3 days course for amoxicillin suspension (oral) instead of 5 days course of co trimoxazole suspension. Amoxicillin suspension proved to be a safe and efficacious treatment for children (aged two to fifty nine months) diseased with fast breathing pneumonia. Moreover, short treatment course for amoxicillin suspension proved to have a positive impact as regards the treatment adherence is concerned. It ultimately leads to cost-effective treatment by avoiding the resistance against the antimicrobials. (Salim Sadruddin et al, 2019).

Non-Severe Pneumonia in Children (2-59 Months)

In the Children Hospital PIMS Islamabad, Pakistan, a study was conducted to check the adherance to treatment guidelines for outpatient children diseased with non-severe Pneumonia. For this, around 380 diseased children were included in the study, and their prescriptions were analyzed (for the correct medical order for the use of amoxicillin and co trimoxazole in non-severe Pneumonia). On concluding the study, it was found that only approx. 46% patients were treated appropriately with the WHO guidelines (for the non-severe Pneumonia), and it depicted that WHO guidelines are not followed to the fullest extent, which is indeed an alarming situation (Shahzad Munir, 2009).

Conclusion

The studies conducted in various areas of Pakistan depicted that the stated standard guidelines are not being followed in Pakistan to the fullest extent. There is an alarming rate of irrational use of the medications that ultimately lead to poor patient outcomes. Therefore, there is an urgent need for the development and implementation of plans/strategies that would be directed towards positive

patient outcomes by following rational use of the drugs. The following describes the need for the implementation of rational use of drugs.

Need for Rational Use of Drugs

Following are the points that are directed towards the rational use of the drug;

- Necessitation of appropriate selection of antibiotic medications for positive patient outcomes.
- Avoid antibiotic misuse that would otherwise lead to antibiotic resistance.
- Check antibiotic overuse.
- Reduce the treatment cost to the patient.
- Development of plans that would reduce stress on the limited health care resources.
- Need for an efficient drug utilization review program to deal one of the major issues, i.e; polypharmacy to avoid irrational use of the medications.
- Resolve non-adherence issues.

Other Hurdles to Irrational Drug Use & Medical Related Problems

- Lack of local or national guidelines for the treatment of Pneumonia in children.
- Prescribers were not found to be following the stated guidelines to the fullest.
- Need for educational strategies for drug utilization review (DUR) is necessary to educate physicians and other health care providers, in order to directly facilitate positive patient outcomes.
- Need for managerial strategies in terms of dispensing strategies and strategies aimed at prescribers.
- Need for economic strategies to avoid inappropriate financial incentives.

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