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Review

Amoxicillin in the Treatment of Mastoiditis: Efficacy, Challenges, and Future Directions

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Received: 30 September 2025; **Revised:** 15 December 2025; **Accepted:** 20 January 2026; **Published:** 28 January 2026

Abstract: Mastoiditis, a serious complication of acute otitis media, primarily affects the pediatric population and requires prompt diagnosis and treatment to prevent severe complications. This review explores the pathophysiology, clinical presentation, diagnostic techniques, and therapeutic approaches for mastoiditis, focusing on the role of amoxicillin in its management. The anatomical connection between the middle ear and mastoid air cells facilitates the spread of infection, which is further influenced by inflammatory processes, bacterial biofilms, and host immune responses. Diagnosis involves a combination of clinical findings, imaging studies such as computed tomography and magnetic resonance imaging, and microbiological cultures to guide targeted antibiotic therapy. Amoxicillin remains the first-line treatment for non-resistant cases owing to its effectiveness against common pathogens, safety profile, and cost efficiency. However, the increasing prevalence of β-lactamase-producing bacteria necessitates the use of amoxicillin-clavulanate in resistant cases. Antibiotic selection should be based on local resistance patterns and patient-specific factors, such as allergies and comorbidities. Surgical interventions, including mastoidectomy, are required in advanced or refractory cases. Future research should focus on developing novel diagnostic tools, optimizing antibiotic regimens, and implementing antimicrobial stewardship programs to combat drug resistance. Global collaboration is essential for establishing standardized guidelines and improving access to high-quality care in resource-limited settings.

Keywords: Mastoiditis; Otitis Media; Amoxicillin; Antimicrobial Therapy; Diagnostic Techniques; Imaging; Antibiotic Resistance

1. Introduction

Mastoiditis, a complication of otitis media, primarily affects the mastoid bone of the ear. It occurs when a middle ear infection spreads to the mastoid air cells, causing inflammation and serious health issues if untreated. Infection spreading from the middle ear to the mastoid air cells can lead to bone destruction and abscess formation, increasing the risk of complications such as intracranial infections [1, 2]. Studies in the United States and Saudi Arabia show acute mastoiditis is common in pediatric populations [1,3].

Mastoiditis presents as ear pain, fever, swelling behind the ear, hearing impairment, and ear discharge. Diagnosis involves clinical examination, imaging studies like computed tomography scans, and culture tests to identify bacteria [4, 5]. Treatment involves broad-spectrum antibiotics followed by culture-specific antibiotics. In cases with complications like intracranial abscesses, surgical intervention, including mastoidectomy or drainage, may be needed [1, 6]. Research shows surgical treatment reduces complications more than conservative or medical management [6].

Mastoiditis can lead to severe complications, including hearing loss, meningitis, brain abscesses, and other intracranial conditions. Studies report that intracranial thrombophlebitis, abscesses, and meningitis have serious outcomes [1, 7]. Data from Israel and the United Kingdom show variations in incidence and management [5, 7]. Preventive efforts should focus on the timely treatment of otitis media. Vaccinations such as pneumococcal vaccines can reduce the occurrence of otitis media and lower the risk [8].

Mastoiditis is a critical complication of otitis media requiring prompt management to prevent serious outcomes. Understanding its pathophysiology, clinical presentation, and treatment are crucial for improving patient outcomes and reducing complications.

This review investigates the clinical manifestations, diagnostic techniques, and therapeutic results of mastoiditis, emphasizing the efficacy of amoxicillin and other antibiotics. This study aimed to explore how early detection and intervention could prevent complications and examine the relevance of anatomical differences and antibiotic resistance patterns in the successful management of mastoiditis.

2. Methodology

This review investigates the clinical manifestations, diagnostic techniques, and therapeutic results of mastoiditis, emphasizing the efficacy of amoxicillin and other antibiotics. This study aimed to explore how early detection and intervention could prevent complications and examine the relevance of anatomical differences and antibiotic resistance patterns in the successful management of mastoiditis. This review presents the findings on mastoiditis, including its clinical manifestations, diagnostic techniques, and treatment approaches. This review draws from peer-reviewed literature, clinical guidelines, and case studies accessed via PubMed, Scopus, and the Web of Science. A search was conducted using terms such as “mastoiditis,” “acute otitis media complications,” “amoxicillin,” “antimicrobial therapy,” and “pneumatization.” This review incorporated English-language studies on the pathophysiology, clinical presentation, diagnostic methods, and treatment options for mastoiditis in children and adults. It focused on imaging techniques, microbiological assessments, and the effectiveness of interventions, such as antibiotic treatments (e.g., amoxicillin) and surgical procedures (e.g., mastoidectomy). The study examined challenges, including antibiotic resistance, anatomical differences, delayed diagnosis, and strategies to improve patient outcomes. Insights from global research, particularly advancements in the last ten years, were organized thematically to offer a holistic view of current practices and emerging trends in mastoiditis management.

3. Role of Timely and Effective Antimicrobial Therapy

Prompt and efficient antimicrobial treatment is crucial for addressing infections, such as acute mastoiditis. Early antimicrobial therapy stops the progression of infection. For mastoiditis, swift action can prevent spread to the mastoid bone and other regions, reducing severe complications such as intracranial abscesses, meningitis, and other infections, leading to morbidity and mortality [1–3].

Effective antimicrobial therapy enhances patient outcomes and reduces morbidity and mortality rates. Research shows that timely treatment leads to faster symptom relief, shorter illness duration, and hospital stays [3,6]. This is vital in pediatric cases, where acute mastoiditis can cause serious complications if not promptly treated [3,5].

Prudent antimicrobial use combats resistant strains. Effective therapy involves choosing the right agent, dose,

and duration, minimizing resistance risk [9,10]. Antimicrobial stewardship programs promote appropriate antibiotic use to fight resistance [11,12].

Timely therapy reduces healthcare expenses by lessening the need for extensive interventions and extended hospital stays [1,6]. Faster recovery yields economic benefits, enabling quicker resumption of activities.

Effective treatment of infectious diseases prevents outbreaks and transmission, and ensures public health safety [13]. In healthcare environments, effective therapy controls the spread of the infection and protects vulnerable populations.

Significance of Amoxicillin in Ear, Nose, and Throat Medicine and Its Importance in Mastoiditis

Amoxicillin, a beta-lactam antibiotic, impedes bacterial cell wall formation and is effective against Gram-positive and Gram-negative bacteria. This broad-spectrum action combats pathogens such as *Streptococcus (S.) pneumoniae* and *Haemophilus (H.) influenzae* in otolaryngological infections [14,15]. Amoxicillin is the initial treatment for acute otitis media (AOM), particularly in children, as it resolves infections and reduces the risk of mastoiditis [14,16]. For mastoiditis caused by untreated middle ear inflammation, amoxicillin may be prescribed if the bacteria are susceptible. In severe cases, it is combined with clavulanic acid for beta-lactamase-producing bacteria [15,17]. Treatment choice must consider the risk of resistance and patient factors [17,18]. Amoxicillin has a favorable safety profile in children with AOM and mastoiditis [14,15]. Antibiotic-resistant strains can reduce efficacy, requiring careful selection [15,17,18]. Patients with penicillin allergies require alternative treatments [17]. Amoxicillin is crucial for managing AOM and preventing mastoiditis progression, with efficacy dependent on bacterial susceptibility [14,15].

4. Pathophysiology and Anatomy

4.1. Anatomy

- Located behind the ear, the mastoid bone features a prominent bony projection called the mastoid process.
- The mastoid process contains air-filled cavities known as mastoid air cells connected to the middle ear cavity through the mastoid antrum [19,20].
- These cavities vary in size and quantity among individuals and are covered with a mucous membrane resembling that of the middle ear. They regulate middle ear pressure and assist in drainage and ventilation [19,20].
- The extent of pneumatization varies considerably and has been examined in relation to age, sex, and anatomical variations [19,21].
- The mastoid bone is close to crucial structures, including the middle and inner ear, sigmoid sinus, and facial nerves. This proximity is important for infections and surgical procedures [22].

4.2. Physiology

- Mastoid air cells regulate the air pressure within the middle ear, which is crucial for proper hearing. This ventilation helps to equalize the pressure across the eardrum, facilitating sound wave transmission [20,23].
- The mastoid process provides structural support and protection of the inner ear components. Its honeycomb-like structure helps absorb and disperse mechanical forces, thereby shielding the ear from harm [20].
- The mastoid bone's connection to the middle ear makes it vulnerable to infections such as mastoiditis, which can result from untreated otitis media. Such infections may lead to the destruction of air cells and complications involving nearby structures [15,24].

4.3. Associated Diseases

Mastoiditis involves inflammation of the mastoid air cells, typically following untreated or severe middle ear infections, and can result in complications owing to its proximity to the brain and venous sinuses [15]. Mastoidectomy, a surgical procedure involving partial removal of the mastoid bone, is often performed to treat chronic ear infections and mastoiditis. Understanding mastoid anatomy is crucial to avoid damaging surrounding structures during surgery [24,25].

5. Mechanisms of Infection Spread

5.1. Connection with the Middle Ear

The anatomical link between the mastoid air cells and the middle ear cavity via the mastoid antrum enables infection spread, particularly in otitis media cases [15, 20]. Eustachian tube inflammation can worsen infection spread by creating an environment conducive to pathogen movement [15,26].

5.2. Inflammatory Process

Middle ear infections can trigger an inflammatory response leading to fluid and pus accumulation, increasing pressure, and facilitating infection extension into the mastoid air cells [27]. The inflammatory process affects the mucosal lining of the mastoid air cells, hindering ventilation and drainage [26,27].

5.3. Bacterial Pathogens and Biofilms

Mastoiditis is often associated with pathogens such as *S. pneumoniae, H. influenzae*, and *Moraxella catarrhalis*. The ability of these bacteria to form biofilms adds complexity, shielding them from host immune responses, and enhancing antibiotic resistance [27]. Research has demonstrated significant biofilm presence in the mastoid mucosa of patients with chronic otitis media patients [27].

5.4. Compromised Immune Response

An impaired immune system can promote pathogen spread from the middle ear to mastoid air cells [15], allowing bacteria to flourish and invade adjacent structures [27].

5.5. Anatomical Variations and Pneumatization

Variations in mastoid bone pneumatization can influence infection susceptibility [20,23]. Poorly pneumatized mastoids may have less effective drainage and ventilation, thus increasing the risk of infection. Excessive pneumatization can present challenges [21].

5.6. Clinical Implications

Table 1 summarizes the common clinical characteristics and their frequencies in pediatric mastoiditis cases. Diagnosis and Treatment: Understanding these mechanisms is crucial for the prompt diagnosis and effective treatment of mastoiditis, which may involve antibiotics and surgical interventions such as mastoidectomy [15,24].

Table 1. Common clinical manifestations of acute mastoiditis in children.

	Symptom	Clinical Description	Frequency
1.	Otalgia (ear pain)	Persistent, often severe	Very common
2.	Postauricular swelling	Erythema, edema, tenderness behind ear	Common
3.	Fever	>38 °C, associated with systemic signs	Common
4.	Otorrhea	Ear discharge due to tympanic membrane perforation	Occasional
5.	Hearing impairment	Conductive loss from effusion or bone changes	Variable
6.	Irritability/malaise	Non-specific, common in children	Frequent

5.7. Prevention

Effective management of otitis media, including timely antimicrobial therapy and addressing eustachian tube dysfunction, is vital to prevent progression to mastoiditis [26].

Mastoid air cell infection primarily results from the spread of pathogens from the middle ear, driven by anatomical connections, inflammatory processes, and anatomical and immunological factors. Understanding these mechanisms is essential for the effective prevention and management of mastoiditis.

5.8. Diagnostic Evaluation

Radiological assessment is crucial for confirming acute mastoiditis and evaluating the extent of the disease and its complications. High-resolution computed tomography (CT) of the temporal bone is preferred because of

its ability to detail bony structures. Common CT findings include filled mastoid air cells, disappeared intercellular septations, merged air cells, and erosion of the mastoid cortex or sigmoid plate, indicating osteitis. CT identifies extracranial complications such as subperiosteal abscesses, middle ear involvement, and ossicular chain erosion, which helps determine the need for surgical intervention [4–7,15].

Magnetic resonance imaging (MRI) is used when intracranial or soft-tissue complications are suspected, as it provides better soft-tissue contrast than CT. MRI findings include hyperintense T2-weighted signals in the mastoid and middle ear cavities, inflamed mucosa enhancement, and epidural or intracranial abscesses. MRI effectively detects venous sinus thrombosis, cerebritis, and meningeal involvement, serving as a complementary tool for the early identification of life-threatening complications in complex mastoiditis [5–7].

6. Treatment Strategies

6.1. Mechanism of Action of Amoxicillin

Amoxicillin, a β-lactam antibiotic, combats bacterial infections by targeting the cell wall, and is crucial for bacterial survival and integrity. Drug action involves key steps:

6.2. Mode of Action

- Amoxicillin targets penicillin-binding proteins (PBPs), which cross-link peptidoglycan layers essential for the bacterial cell wall. By attaching to PBPs, amoxicillin weakens the strength of the cell wall.
- The β-lactam ring in amoxicillin mimics the natural substrate of PBPs, thus enabling permanent bonding. This prevents PBPs from functioning during the transpeptidation step, which is crucial for peptidoglycan cross-linking. Structural studies show this interaction [28,29].
- Inhibition of PBPs disrupts transpeptidation and compromises the cell wall structure. Impaired peptidoglycan cross-linking renders the bacterial cell wall unable to withstand internal osmotic pressure [30].
- A weakened cell wall prevents the bacteria from maintaining osmotic pressure, leading to cell lysis and death. The structural features of β-lactam antibiotics enhance this mechanism [28,30].

6.3. Resistance and Clinical Considerations

- Widespread use of amoxicillin has led to bacterial strains producing β-lactamase enzymes, which break down the β-lactam ring, making the antibiotic ineffective. Amoxicillin is often paired with β-lactamase inhibitors, such as clavulanic acid [28].
- Pairing amoxicillin with β-lactamase inhibitors broadens its range of activity and is effective against resistant strains. This approach is crucial for treating infections caused by β-lactamase-producing pathogens [28].
- Amoxicillin inhibits bacterial cell wall synthesis by targeting PBPs, disrupting peptidoglycan crosslinking, and causing bacterial cell lysis. Understanding these mechanisms is essential for optimizing their clinical use and addressing antibiotic resistance.

7. Effectiveness against Typical Mastoiditis Pathogens

Amoxicillin, a β-lactam antibiotic, is crucial for the treatment of mastoiditis because of its effectiveness against common pathogens. Understanding its efficacy is vital to enhancing patient outcomes.

7.1. Range of Effectiveness

7.1.1. Gram-Positive Bacteria

***Streptococcus pneumoniae*:** The leading cause of mastoiditis, particularly after middle ear infections. Amoxicillin is effective against penicillin-susceptible *S. pneumoniae*. However, resistance, especially in serotype 19A, has increased since vaccine introduction [31] (**Table 2**).

***Streptococcus pyogenes*:** Less frequently linked to mastoiditis; *S. pyogenes* generally responds well to amoxicillin due to its β-lactam sensitivity [32].

Table 2. Typical bacterial pathogens in mastoiditis and amoxicillin susceptibility.

	Pathogen	Frequency	Amoxicillin Susceptibility	Key Findings
1.	*Streptococcus pneumoniae*	Most common (esp. post-acute otitis media)	High (except resistant serotypes such as 19A)	Pneumococcal conjugate vaccine vaccination has altered prevalence
2.	*Haemophilus influenzae*	Common	Susceptible if non-β-lactamase producing	β-lactamase strains require amox-clav
3.	*Moraxella catarrhalis*	Less common	Often resistant	Combination therapy required
4.	*Streptococcus pyogenes*	Uncommon	Highly susceptible	Rare but severe presentations
5.	*Fusobacterium necrophorum*	Emerging in complicated cases	Variable	Often requires extended/targeted therapy

7.1.2. Gram-Negative Bacteria

***Haemophilus influenzae*:** Effective against non-β-lactamase-producing *H. influenzae*. The rise in β-lactamase-producing variants often necessitates amoxicillin-clavulanate [28,33] (**Table 2**).

***Moraxella catarrhalis*:** Frequently produces β-lactamase, which requires combination therapy with a β-lactamase inhibitor [33].

7.1.3. Emerging Pathogens

***Fusobacterium necrophorum*:** Recognized in complex mastoiditis cases, this anaerobic bacterium requires specialized treatment due to potential complications [34].

7.2. Medical Considerations

Resistance patterns: The prevalence of β-lactamase-producing strains requires careful selection of antibiotics. Amoxicillin-clavulanate is recommended to improve efficacy, especially in areas with high resistance rates [15,28].

Initial treatment: When the pathogen is unknown, amoxicillin-clavulanate is often prescribed because of its broad-spectrum and enhanced activity against resistant organisms [35].

Safety profile: Amoxicillin is well-tolerated and has a good safety record, making it a preferred option for treating mastoiditis in both children and adults [15].

Amoxicillin, especially clavulanate, is effective against typical mastoiditis. Its broad spectrum and improved efficacy against resistance make it a reliable choice. Understanding local resistance patterns and selecting appropriate initial therapies are crucial.

8. Pharmacokinetics and Pharmacodynamics in Otologic Infections

Understanding antibiotic pharmacokinetics and pharmacodynamics is crucial for managing ear infections, such as otitis media and mastoiditis. These concepts guide dosing strategies to achieve effective drug concentrations at the infection site, enhance bacterial elimination, and reduce resistance.

8.1. Pharmacokinetics

- Antibiotics such as amoxicillin have high oral bioavailability, ensuring adequate systemic levels for effective penetration into the middle ear and mastoid air cells. Extended-release formulations can enhance adherence and sustain therapeutic effects [36].
- Therefore, effective tissue penetration is crucial. Amoxicillin shows good distribution in the middle ear and mastoid tissues, reaching concentrations that combat common pathogens. The volume of distribution balances the systemic distribution and targeted tissue penetration, which is crucial for localized infections such as mastoiditis [15,31].
- Most antibiotics used for ear infections undergo minimal liver metabolism and reduce drug-drug interaction risks. Renal excretion necessitates dose adjustments in patients with impaired kidney function to prevent drug accumulation and toxicity [37].

8.2. Pharmacodynamics

- Beta-lactam antibiotics, including amoxicillin, exhibit time-dependent killing effects. Their effectiveness is correlated with the duration of drug concentrations exceeding the minimum inhibitory concentration (MIC) of the pathogen. Maintaining drug levels above the MIC is essential for optimal bacterial eradication [38,39].

- Antibiotics such as aminoglycosides and fluoroquinolones display concentration-dependent killing, where higher concentrations result in faster bacterial death. Achieving peak concentrations is crucial for the treatment of ear infections [38].
- Some antibiotics show a post-antibiotic effect, suppressing bacterial growth even after the levels fall below the MIC. This property allows for less frequent dosing, potentially improving adherence [38].

8.3. Clinical Implications

Integrating the PK/PD principles is essential for optimizing antibiotic therapy for ear infections. This involves selecting dosing regimens that maximize therapeutic outcomes, while minimizing toxicity and resistance. Time-dependent antibiotics may require more frequent administration, whereas concentration-dependent antibiotics may require higher doses administered less frequently. Customizing therapy based on factors such as age, kidney function, and infection severity is crucial for effective treatment [36].

9. Amoxicillin as Monotherapy

9.1. Clinical Studies and Evidence

Numerous randomized controlled trials (RCTs) have confirmed the efficacy of amoxicillin in treating uncomplicated for AOM, particularly in pediatric populations. These studies demonstrated effective symptom resolution and bacterial eradication, notably against *S. pneumoniae* and non-beta-lactamase-producing *H. influenzae*. Introduction of pneumococcal conjugate vaccines has altered the prevalence of specific serotypes, but amoxicillin remains effective against many strains of *S. pneumoniae* [31,40,41].

A systematic review protocol was designed to further evaluate the effectiveness of amoxicillin alone for uncomplicated AOM, indicating ongoing research interest and the need for continuous evaluation of its efficacy in light of changing pathogen profiles and resistance patterns [42].

9.2. Comparative Studies

Comparative studies have shown that amoxicillin is as effective, if not more so, than other antibiotics for uncomplicated cases. Its targeted spectrum helps minimize its impact on normal flora and reduces the risk of antibiotic resistance [31,43]. Moreover, a large cohort study found no significant difference in treatment failure rates between amoxicillin and amoxicillin-clavulanate for pediatric acute sinusitis, suggesting the adequacy of amoxicillin in many uncomplicated cases [17].

9.3. Dosage and Duration Recommendations

9.3.1. Dosage

Children: The recommended dosage for pediatric patients is typically 80–90 mg/kg/day, which is divided into two doses. This higher dosage is aimed at overcoming potential resistance, particularly from S. pneumoniae [36,43] (**Table 3**).

Table 3. Dosage and duration recommendations for amoxicillin.

	Patient Group	Dosage (Typical)	Duration	Key Findings
1.	Children	80–90 mg/kg/day in 2 divided doses	5–7 days (≥2 yrs, mild cases)/10 days (<2 yrs or severe)	Weight-based dosing crucial
2.	Adults	500–875 mg every 12 h	7–10 days	Adjust in renal impairment

Adults: Standard dosages ranged from 500 mg to 875 mg every 12 h. Dosing adjustments may be necessary based on the severity of the infection and patient-specific factors such as kidney function and body weight [43].

9.3.2. Duration

Children: A 5–7 day course is often sufficient for children over 2 years of age with mild to moderate symptoms. For children under 2 years or those with severe symptoms, a 10-day course is recommended to ensure complete resolution of the infection [17,43].

Adults: The typical treatment duration is 7–10 days, depending on clinical response and infection severity [43] (**Table 3**).

Amoxicillin remains a highly effective monotherapy for uncomplicated otologic infections, as supported by substantial clinical evidence and guideline endorsements. Its favorable safety profile and well-defined dosage and duration parameters justify its continued use as a first-line treatment. Adjusting treatment protocols based on patient age, symptom severity, and local resistance patterns is essential for optimizing clinical outcomes.

10. Combination Therapies with Amoxicillin

The combination of amoxicillin with other therapies enhances its effectiveness, particularly against resistant bacteria. This strategy uses clavulanic acid to combat β-lactamase-producing bacteria and explores the synergistic effects of antibiotics, such as macrolides or cephalosporins.

10.1. Role of Clavulanic Acid in Addressing β-Lactamase-Producing Bacteria

As a β-lactamase inhibitor, clavulanic acid protects amoxicillin from breakdown by the β-lactamase enzymes produced by certain bacteria. By inhibiting these enzymes, clavulanic acid broadens amoxicillin's range, enabling it to target β-lactamase-producing bacteria like *H. influenzae* and *Moraxella catarrhalis*, common in ear and respiratory infections [41,43].

The amoxicillin-clavulanic acid combination has shown enhanced clinical results in infections in which β-lactamase production is a factor. Research indicates that while amoxicillin-clavulanate does not significantly outperform amoxicillin alone in treating acute sinusitis, it is associated with more digestive side effects (SEs) [17]. This highlights the need to weigh the advantages against potential adverse reactions when selecting this combined therapy.

10.2. Synergistic Effects with Macrolides and Cephalosporins

10.2.1. Macrolides

Macrolides such as azithromycin inhibit bacterial protein synthesis. When used with amoxicillin, which targets cell wall formation, these antibiotics offer wide activity and potential synergistic effects. This combination can benefit patients with mixed infections or atypical pathogens. However, its routine use is limited because of resistance concerns and specific activity profiles [41].

10.2.2. Cephalosporins

Cephalosporins and amoxicillin are β-lactam antibiotics. Cephalosporins often provide broader coverage against certain resistant strains, including those producing extended-spectrum β-lactamases. In severe infections or those involving diverse bacterial flora, cephalosporins may be combined with amoxicillin to enhance bacterial coverage, especially in hospitals, where resistance is more prevalent [43].

Combination therapies with amoxicillin combat bacterial resistance and improve treatment outcomes. Clavulanic acid enhances the efficacy of amoxicillin against β-lactamase-producing bacteria, whereas combinations with other antibiotics can offer synergistic benefits in specific scenarios. The selection of combination therapy should consider infection type, patient factors, and local resistance patterns to ensure optimal treatment while minimizing resistance development. This approach is supported by studies on the impact of pneumococcal vaccines on serotype distribution and resistance [14,31].

11. Effectiveness of Amoxicillin vs Cephalosporins and Fluoroquinolones

To assess the efficacy of amoxicillin versus cephalosporins and fluoroquinolones for conditions such as acute otitis media (AOM) and bacterial infections, it is crucial to consider their effectiveness, safety, antibiotic resistance trends, and clinical recommendations.

11.1. Amoxicillin

Effectiveness: Amoxicillin is highly effective against many *S. pneumoniae* and *H. influenzae* strains that don't produce β-lactamase, making it the preferred treatment for uncomplicated AOM, especially in children, due to its

targeted action, cost-efficiency, and safety profile [41,43]. A systematic review protocol highlighted its established role in current treatment strategies [42].

Safety and resistance: Amoxicillin is generally well-received with minimal SEs. However, β-lactamase-producing bacteria can reduce its effectiveness, sometimes requiring clavulanic acid [17,41]. The amoxicillin-clavulanate combination may increase digestive issues and fungal infections, as seen in pediatric sinusitis research [17].

11.2. Cephalosporins

Effectiveness: Cephalosporins, such as cefuroxime and cefdinir, offer broader protection against resistant strains, and are used when amoxicillin is ineffective or in cases of penicillin allergy. They can combat a wide range of β-lactamase-producing bacteria [43]. Studies suggest their potential for wider use than amoxicillin in conditions such as chronic periodontitis [44].

Safety and resistance: Cephalosporins are generally safe, but can cause digestive discomfort and, rarely, allergic reactions. Their higher cost compared to amoxicillin may affect prescription decisions, especially in resource-limited settings [44].

11.3. Fluoroquinolones

Effectiveness: Fluoroquinolones such as levofloxacin and ciprofloxacin are effective against a wide array of bacteria, including atypical pathogens, and are reserved for severe infections or resistant organisms [43].

Safety and resistance: Fluoroquinolones carry the risk of serious adverse effects, including tendon inflammation, nerve damage, and heart rhythm disturbances, limiting their use as first-line treatment. Their potential to foster antibiotic resistance is significant, leading to recommendations for their cautious use [43].

11.4. Comparative Studies and Guidelines

Effectiveness: Comparative research supports the use of amoxicillin for uncomplicated infections, especially in pediatric patients. Cephalosporins are often used as second-line therapy because of their broad spectrum, whereas fluoroquinolones are reserved for complex cases or resistant pathogens [43,45].

Guidelines: Clinical guidelines endorse amoxicillin as the initial treatment for uncomplicated AOM and similar infections, citing its efficacy, safety, and narrow spectrum of action to minimize normal flora disruption. Cephalosporins may be recommended for non-severe penicillin allergy or treatment failure, while fluoroquinolones are reserved for specific indications owing to their SEs [41,43].

Amoxicillin remains fundamental in the treatment of uncomplicated bacterial infections owing to its effectiveness, safety, and cost efficiency. Although cephalosporins and fluoroquinolones offer broader coverage and are effective in specific scenarios, their use is often limited by cost, safety concerns, and antibiotic resistance.

12. Safety and Tolerability Profile Compared to Amoxicillin vs Cephalosporins and Fluoroquinolones

When evaluating the safety and tolerability of amoxicillin compared to cephalosporins and fluoroquinolones, it is essential to consider SEs, allergic responses, and patient factors. This evaluation draws on recent studies from a more comprehensive perspective.

12.1. Amoxicillin

Safety Profile: Amoxicillin has a positive safety record. Typical adverse reactions include mild digestive issues such as nausea, vomiting, and diarrhea. Allergic reactions are possible because of their β-lactam structure but are uncommon. Research shows that many reported penicillin allergies are not verified upon testing, supporting their use as a primary treatment, especially in children [41,43].

Tolerability: Amoxicillin is well-accepted across age groups, leading to high compliance rates. It is the preferred antibiotic for simple infections, with guidelines recommending high-dose amoxicillin for conditions such as acute otitis media and barring confirmed allergies [41,43].

12.2. Cephalosporins

Safety: Cephalosporins, including cefixime and cefuroxime, typically cause gastrointestinal SEs that are similar to those of amoxicillin. They are generally safe, well-tolerated, and suitable for patients with non-severe penicillin allergies. There is a 5–10% risk of cross-reactivity in penicillin-allergic patients, which decreases with second- and third-generation cephalosporins [44,46].

Tolerability: These antibiotics are used when broader bacterial coverage is needed or when amoxicillin is contraindicated. Their wider spectrum can be beneficial but may result in higher costs and less targeted therapy, affecting patient adherence [44,46].

12.3. Fluoroquinolones

Safety: Fluoroquinolones are linked to serious adverse effects, such as tendinitis, tendon rupture, peripheral neuropathy, and CNS effects, such as dizziness and confusion. They can also extend the QT interval and increase the risk of cardiac arrhythmias. These SEs have prompted regulatory warnings, restricting their use as first-line treatment [47,48].

Tolerability: Given their risk profiles, fluoroquinolones are reserved for cases in which other antibiotics are ineffective or contraindicated. Their use is limited to specific indications owing to safety concerns despite their broad-spectrum effectiveness [47,48].

The safety and tolerability of amoxicillin make it a preferred option for uncomplicated infections, especially in pediatric and general practice settings. Cephalosporins are suitable for patients with allergies or specific needs, albeit at a higher cost. Fluoroquinolones are restricted to more complex infections owing to their serious adverse effects.

13. Side Effects and Challenges in Amoxicillin Use

Amoxicillin, a common antibiotic, is known for its efficacy and safety. However, their use is associated with several challenges and potential SEs. Understanding these aspects is crucial for enhancing treatment outcomes and reducing patient risks.

13.1. Side Effects

- **Digestive system disturbances:** Amoxicillin often causes mild, self-resolving digestive issues such as nausea, vomiting, diarrhea, and stomach discomfort. This can be alleviated by consuming medication with food. Rarely, more serious conditions, such as antibiotic-associated colitis, may occur, requiring observation and treatment [49].
- **Hypersensitivity reactions:** Allergic responses range from mild skin rashes to severe reactions, such as anaphylaxis, although genuine penicillin allergies are uncommon. Cross-reactivity with other β-lactam antibiotics is possible, but less frequent with newer cephalosporins [46, 50]. One case reported potential anaphylaxis induced by amoxicillin transfer through oral sex, emphasizing the need for hypersensitive individuals [51].
- **Secondary infections:** Disruption of normal flora by amoxicillin can lead to secondary infections such as oral or vaginal candidiasis. Monitoring for signs of these infections is advisable, especially during extended use [17].
- **Liver and kidney effects:** Rarely, amoxicillin can cause liver dysfunction and kidney issues, including elevated liver enzyme levels and interstitial nephritis. Drug-induced liver injury has been linked to amoxicillin alone and in combination with clavulanic acid [52,53]. Monitoring is recommended for patients with preexisting liver or kidney disease.

13.2. Difficulties in Amoxicillin Usage

- **Antibiotic resistance:** The emergence of resistant bacterial strains presents a challenge to the effectiveness of amoxicillin. A combination with clavulanic acid is used to combat this resistance, though it may increase gastrointestinal SEs [17,41,43].
- **Incorrectly diagnosed allergies:** Many individuals report unconfirmed penicillin allergies, leading to unnecessary use of broad-spectrum antibiotics. Confirmatory allergy testing can ensure the appropriate selection [46].
- **Treatment adherence:** Adherence issues may arise owing to dosing frequency, treatment duration, or SEs. Simplifying dosing schedules and providing clear instructions can improve adherence [41].

- **Public health issues:** The excessive and improper use of amoxicillin contributes to antibiotic resistance, highlighting the importance of antimicrobial stewardship programs to promote appropriate use. This is crucial for maintaining the efficacy of amoxicillin and other antibiotics [43].

Amoxicillin remains valuable for treating bacterial infections because of its safety and effectiveness. However, potential SEs and challenges such as resistance development, misdiagnosed allergies, and patient adherence must be addressed.

14. Challenges in Management

14.1. Risk of Resistance: Role of Antibiotic Stewardship in Reducing Resistance

The global health crisis associated with antibiotic resistance is exacerbated by inappropriate and excessive antibiotic use, including amoxicillin. Antibiotic stewardship initiatives are vital for maintaining effectiveness and preventing resistant bacterial strains.

14.2. Resistance Development Pathways

Bacteria can acquire resistance through β-lactamase enzymes that break down antibiotics, such as amoxicillin, modify target sites, and use efflux pumps to remove antibiotics from cells. These adaptations can render antibiotics ineffective, complicating treatments and increasing the likelihood of therapeutic failure [41,43,54].

14.3. Antibiotic Stewardship Importance

14.3.1. Encouraging Proper Usage

Antibiotic stewardship programs aim to enhance antibiotic utilization by ensuring prescription only when necessary and when appropriate. This involves choosing the correct antibiotic, dosage, and treatment duration to combat infections, while minimizing unnecessary exposure to broad-spectrum antibiotics. High-dose amoxicillin is recommended for certain infections to overcome intermediate resistance, reserving broader-spectrum antibiotics for confirmed resistant cases [41,43,55].

14.3.2. Enhancing Knowledge and Awareness

Education forms the foundation of stewardship. Healthcare professionals and patients must be informed about the dangers of antibiotic overuse and misuse and the importance of completing prescribed courses. This educational effort helps reduce unnecessary antibiotic use, particularly for viral infections [56,57].

14.3.3. Guideline Implementation

Stewardship initiatives promote adherence to clinical guidelines that recommend evidence-based first-line treatment. These guidelines help standardize care and reduce variability in antibiotic prescriptions. For instance, guidelines specify using amoxicillin or amoxicillin-clavulanate for otitis media in children, aligning prescriptions with resistance trends [41,43].

14.3.4. Observation and Surveillance

Monitoring antibiotic use and resistance patterns is crucial for informing stewardship efforts and for guiding policy decisions. Surveillance data can identify trends and inform timely adjustments to treatment protocols, thereby enhancing the effectiveness of stewardship strategies [55,57].

14.3.5. Scientific Inquiry and Innovation

Therefore, research on new antibiotics and alternative therapies is essential. Developing rapid diagnostic tests to distinguish between bacterial and viral infections can reduce unnecessary antibiotic use. This research is a critical component of stewardship that supports long-term antibiotic efficacy [57].

15. Patient-Specific Factors: Allergies, Comorbidities, and Contraindications

In prescribing antibiotics, such as amoxicillin, evaluating patient-specific factors, including allergic reactions, health conditions, and contraindications, is crucial for safe and effective treatment. These considerations determine the appropriate antibiotic and treatment approaches.

15.1. Allergic Reactions

- Many cases of penicillin allergy have been reported, but many cases remain unverified. Differentiating genuine allergies from adverse effects prevents unnecessary avoidance of penicillin and first-generation cephalosporins. Research shows up to 90% of children with reported penicillin allergies can safely use these antibiotics after proper assessment [58–60].
- There is a possibility of shared sensitivity between penicillins and cephalosporins, especially first-generation cephalosporins, but this is uncommon. Newer cephalosporins are often safe for patients with non-severe penicillin allergies [50].
- For confirmed penicillin allergies, alternatives such as macrolides or specific cephalosporins may be considered based on allergy severity and infection type [58,61,62].

15.2. Existing Health Conditions

- **Impaired kidney function:** Amoxicillin is primarily eliminated through the kidneys; therefore, dosages must be adjusted for patients with kidney impairment to avoid toxicity [43].
- **Liver dysfunction:** Amoxicillin can cause elevated liver enzyme levels or liver dysfunction, requiring monitoring in patients with pre-existing liver conditions. Combined with clavulanic acid, liver-related side effects increase [41].
- **Digestive system disorders:** Antibiotics, including amoxicillin, can disrupt gut bacteria, increasing the risk of Clostridium difficile infection, especially in patients with gastrointestinal disorders. Probiotics or alternative antibiotics may be considered for high-risk patients [28].

15.3. Contraindications

15.3.1. Severe Allergic Reactions

Amoxicillin should not be used in individuals with a history of serious allergic reactions to penicillin, such as anaphylaxis. Confirmed allergic reactions require the use of alternative classes [61].

15.3.2. Specific Drug Interactions

Amoxicillin can increase methotrexate levels, leading to toxicity. Monitoring and dose adjustment are necessary [50]. Amoxicillin may intensify oral anticoagulants, such as warfarin, requiring close monitoring of blood clotting parameters to prevent bleeding complications [50].

Prescribing amoxicillin requires evaluation of patient-specific factors to ensure safe and effective treatment. This personalized approach optimizes outcomes and minimizes adverse reactions.

16. Pediatric vs Adult Use of Amoxicillin

In treating pediatric mastoiditis with amoxicillin, dosage modifications and tolerability are crucial, differing from adult treatments due to physiological and developmental variances. As a complication of acute otitis media, mastoiditis requires careful antibiotic management in children to avoid serious sequelae such as hearing impairment or intracranial infections [1,43].

16.1. Pediatric Amoxicillin Usage

Dosage Modifications

Weight-based dosing: Amoxicillin dosing in pediatric patients is determined by body weight to ensure therapeutic effectiveness while reducing adverse reactions. For severe infections such as mastoiditis, higher doses (80–90 mg/kg/day) are typically recommended to achieve adequate tissue penetration and combat resistant strains of

Streptococcus pneumoniae [36,43].

Pharmacokinetics and formulation: Child-friendly amoxicillin formulations enable precise dosing and ease of administration, addressing pharmacokinetic considerations and practical challenges in pediatric populations [36,63].

16.2. Adult Amoxicillin Usage

16.2.1. Dosage Modifications

Standard dosing: Adults typically receive fixed dosing regimens, with dosages usually ranging from 500 mg to 1 g every 8 to 12 h, depending on infection severity and patient-specific factors such as renal function [62].

Consideration for comorbidities: Adults may require dosage adjustments due to comorbidities such as renal impairment, which is less frequently a concern in pediatric cases [52].

16.2.2. Tolerability

Gastrointestinal and allergic reactions: Adults may experience gastrointestinal side effects and may be more susceptible to allergic reactions due to cumulative exposure over time, necessitating a thorough allergy history and monitoring [50,52].

16.3. Considerations in Pediatric Mastoiditis

16.3.1. Timely Diagnosis and Treatment

Prompt and accurate diagnosis is vital to prevent serious complications in pediatric mastoiditis. Amoxicillin is often used as the initial treatment strategy [1].

16.3.2. Multidisciplinary Approach

A comprehensive treatment approach often involves collaboration among pediatricians, otolaryngologists, and infectious disease specialists to ensure optimal care for pediatric patients [1].

16.3.3. Hospitalization and Intravenous Therapy

In severe cases, or when there is a lack of response to oral antibiotics, hospitalization and intravenous therapy may be necessary. Broader-spectrum antibiotics, such as amoxicillin-clavulanate, may be used, highlighting the need for tailored treatment plans [17].

Amoxicillin is effective in treating pediatric mastoiditis but requires specific considerations for dosage and tolerability. Weight-based dosing and efforts to minimize side effects are crucial in children, whereas in adults, fixed dosing and comorbidities play a more prominent role.

17. Medical Management vs Surgical Intervention

In uncomplicated acute mastoiditis identified early without radiological or neurological issues, the initial treatment is medical, involving broad-spectrum intravenous or high-dose oral antibiotics, with amoxicillin or amoxicillin-clavulanate as the preferred choice based on resistance trends. Patients showing improvement within 48 h, including decreased fever, pain, and postauricular swelling, can continue medical treatment under observation. This approach is suitable for patients without bone destruction, subperiosteal abscess, intracranial spread, facial nerve involvement, or venous sinus thrombosis on imaging [6,15,35].

Surgery is necessary when medical treatment fails or complications arise at diagnosis. Indications for surgery include poor response to antibiotics, signs of coalescent mastoiditis with bone erosion, subperiosteal abscess, intracranial complications (epidural or brain abscess, meningitis, sigmoid sinus thrombosis), facial nerve palsy, or worsening hearing loss. Procedures range from myringotomy with or without tympanostomy tube to cortical or modified radical mastoidectomy based on disease severity. Early surgical intervention in complicated cases reduces morbidity and prevents life-threatening outcomes, emphasizing the need for timely escalation based on clinical assessments [6,24,64].

18. Resistance Trends

Recent findings have shown increasing antimicrobial resistance among mastoiditis-causing bacteria, notably *S. pneumoniae* and *H. influenzae*, with regional differences. Research from North America and Europe has shown an increase in penicillin-resistant *S. pneumoniae* due to serotype replacement after the introduction of the pneumococcal conjugate vaccine, particularly serotype 19A [31,40,41]. In South Asia, the Middle East, and parts of Africa, there remains higher sensitivity to amoxicillin, although β-lactamase producing H. influenzae and Moraxella catarrhalis limit amoxicillin's effectiveness in severe cases [17,43].

These variations highlight the need for region-specific treatment strategies. Data from Israel, Saudi Arabia, and Southern Europe show increasing β-lactamase-producing bacteria and anaerobic pathogens, such as Fusobacterium necrophorum, in complex pediatric mastoiditis [3,7,34]. Studies from Scandinavia and Western Europe have shown stable resistance patterns due to antimicrobial stewardship practices [41,55]. These findings emphasize the importance of using local antibiograms and resistance surveillance data for initial antibiotic choices, switching to amoxicillin-clavulanate when resistance is suspected. Incorporating regional resistance data into clinical guidelines is crucial for optimizing outcomes and reducing broad-spectrum antibiotic use.

19. Future Directions and Emerging Trends

Amoxicillin treatment is evolving and driven by novel formulations, surgical integration, and diagnostic enhancements. This overview explores these domains and their potential impact on medical practices.

19.1. Advancements in Amoxicillin Formulations

Research on extended-release amoxicillin aims to enhance patient compliance and treatment efficacy. Scientists are exploring advanced delivery methods, including lipid nanoparticles, to shield amoxicillin from stomach acid and target infection sites, such as the gastric mucosa [65]. These innovations are crucial for addressing infections, such as Helicobacter pylori, where drug stability and concentration at the infection site are critical. Polymeric nanoparticles and composite hydrogels offer controlled pH-responsive release profiles, potentially boosting the effectiveness of amoxicillin in acute and chronic infections [66,67]. These formulations aim to reduce adverse effects and dosing frequency, and improve patient adherence.

19.2. Amoxicillin's Integration with Advanced Surgical Techniques for Mastoiditis

In mastoiditis cases where conservative treatments fail, combining amoxicillin with surgical procedures, such as mastoidectomy, is crucial for comprehensive infection management. This integrated approach ensures the thorough clearance of residual infections and minimizes postoperative complications. Research indicates that a significant proportion of mastoiditis cases require surgical intervention, underscoring amoxicillin's importance in perioperative care [64,68]. Such combination therapies exemplify a multidisciplinary strategy for maximizing patient outcomes.

19.3. Advancements in Diagnostic Tools for Optimal Early Antibiotic Selection

Rapid and accurate diagnostic tools are used to transform the early selection of antibiotics. Point-of-care tests and molecular diagnostics enable rapid differentiation between bacterial and viral infections, facilitating timely antibiotic prescriptions. This helps to reduce unnecessary antibiotic use and combat resistance [68]. Progress in genomics and proteomics has enabled the identification of specific pathogens and their resistance patterns, paving the way for tailored antibiotic therapies. These innovations promote better stewardship of antibiotics, such as amoxicillin, preserving their effectiveness for future use.

Amoxicillin therapy is transforming owing to advancements in drug formulations, integrative treatment approaches, and diagnostic technologies. Extended-release formulations show promise in improving adherence and therapeutic efficacy, while combining antibiotics with surgical interventions can enhance outcomes in complex cases such as mastoiditis.

20. Recommendations

- To prevent mastoiditis, healthcare systems should focus on the early identification and treatment of acute otitis media through educational initiatives for medical professionals and caregivers, emphasizing prompt symptom recognition and medical care. Routine administration of pneumococcal and Haemophilus influenzae type b vaccines should be encouraged to reduce otitis media occurrence.
- Mastoiditis diagnostic procedures should combine advanced imaging methods, such as computed tomography and magnetic resonance imaging, with microbiological analysis for a precise diagnosis and targeted treatment. Standardizing these procedures across medical facilities can enhance the diagnostic accuracy and treatment results. Training programs should improve clinicians' skills in interpreting imaging findings and handling complex cases.
- The importance of amoxicillin in the management of mastoiditis should be emphasized as an initial treatment for non-resistant cases. National and regional antibiotic guidelines should advocate for its use owing to its safety, effectiveness, and cost efficiency. Combination therapy with clavulanic acid should be recommended in areas with high amoxicillin resistance. Ongoing monitoring of resistance patterns and public education on appropriate antibiotic use are crucial to maintain the efficacy of amoxicillin.
- Antimicrobial stewardship initiatives are vital for addressing antibiotic resistance in mastoiditis management, focusing on suitable antibiotic selection, dosage, and duration based on local resistance trends. Alternative treatments, including combination therapies and novel antimicrobials, should be investigated and integrated into clinical practice. Future studies should examine the impact of anatomical variations, host immune responses, and pathogen biofilms on mastoiditis progression and treatment resistance. International cooperation is encouraged to facilitate large-scale studies and develop global guidelines. Efforts should be made to improve access to diagnostic and treatment resources in underserved regions to reduce disparities in care and outcomes.

21. Conclusions

Mastoiditis remains a serious complication of acute otitis media in children, for which early detection and prompt treatment are crucial. This overview highlights the complexity of the condition, influenced by anatomical links between the middle ear and mastoid bone, and the challenges posed by antibiotic resistance and delayed interventions. Clinical signs of mastoiditis, including otalgia, edema, pyrexia, and potential hearing impairment, require swift recognition and appropriate diagnosis for effective management.

Advancements in diagnostic techniques, particularly computed tomography and magnetic resonance imaging, have improved the identification of mastoiditis and its complications. However, imaging must be supplemented by microbiological cultures to tailor the antibiotic therapy. Research indicates that combining clinical, radiological, and microbiological data is essential for an accurate diagnosis and optimal treatment.

Amoxicillin is key in treating mastoiditis because it is effective against common pathogens, such as *S. pneumoniae* and *H. influenzae*. Its safety, cost-effectiveness, and availability make it the preferred initial choice for pediatric and adult patients. However, the rise of β-lactamase-producing bacteria necessitates the use of amoxicillin-clavulanate in resistant cases, emphasizing the need to monitor local resistance patterns.

Despite advances in diagnosis and treatment, challenges remain in combating antimicrobial resistance and ensuring high-quality care in resource-limited settings. Further research and global collaboration are needed to standardize the diagnostic protocols, treatment regimens, and prevention strategies. Efforts to reduce the prevalence of otitis media through immunization and public health initiatives can significantly lessen the global burden of mastoiditis.

Funding

This work received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Data are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

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