JOURNAL OF INTERNATIONAL CRISIS AND RISK COMMUNICATION RESEARCH
ISSN: 2576-0017
2024, VOL 7, NO S9

An Overview of the Susceptibility Testing of Pharyngeal Group A Streptococcus Pyogenes

Maha Hussein Shararah[1], Meshary Waheeb Albasrawi[2], Rayan Faisal Khyami[3], Faisal Yhaya Juhali[4], Amro Abdullah Alghamdi[5], Fatemah Mohamad Hussin Namazi[6], Mohammed Fawaz Alghufayri[7], Saad Fawaz Bin Khatim Alghufairy[8], Faisal Masoud Alshalihi[9], Samer Muidh W Alsulami[10], Faisal Ahmad Tashkandi[11], Suwaylih Ayidh Saleh Al Juaid[12], Rayan Hasan Abdelah Alqurashi[13], Sana Mohsen Abo Eid[14], Mohammed Ahmed Mohammed Almalki[15]

[1]Medical laboratory Specialties, King Salman Medical city, General, Hospital Laboratory
[2]King Abdulaziz Hospital in Makkah, Medical laboratory technician
[3]King Abdulaziz Hospital in Makkah, Medical laboratory technician
[4]Laboratory specialist, King Abdulaziz Hospitial - Taif-Saudi Arabia
[5]Laboratory tech, King Abdullah Medical city
[6]Hira General Hospital, Medical Laboratory Technician
[7]Lab Technician, King Abdullah Medical City
[8]Medical Laboratory Technician, Maternity and children hospital
[9]Medical Laboratory specialist, Maternity and children hospital
[10]King Abdulaziz Hospital in Makkah, Medical laboratory technician
[11]Laboratory Speciaalist, Executive management of supply chains in the Makkah cluster
[12]Laboratory Speciaalist, Executive management of supply chains in the Makkah cluster
[13]King Abdullah Medical City, Laboratory technician
[14]Lab tech, Hera General Hospital
[15]Lab specialist, King Abdulaziz Hospital in Mecca

Introduction

Group A *Streptococcus pyogenes* (GAS), a β-hemolytic Gram-positive bacterium, is one of the most significant human pathogens globally. It is the primary causative agent of bacterial pharyngitis, a common condition that affects millions of individuals annually, particularly children aged 5–15 years. GAS pharyngitis accounts for approximately 20–30% of sore throat cases in pediatric populations and 5–15% in adults [1]. The clinical relevance of GAS infections extends beyond the acute illness, as untreated or inadequately treated pharyngitis can lead to immune-mediated complications such as acute rheumatic fever, rheumatic heart disease, and post-streptococcal glomerulonephritis, all of which pose substantial public health burdens, particularly in low-resource settings [2,3].

The management of GAS pharyngitis relies on appropriate antimicrobial therapy, not only to resolve symptoms but also to prevent complications and reduce transmission within communities. Penicillin has been the cornerstone of treatment for GAS infections since the 1940s due to its high efficacy, safety profile, and the absence of resistance in GAS strains. However, alternative antibiotics, including macrolides, clindamycin, and cephalosporins, are used for patients with penicillin allergies or for those who experience treatment failures. The increasing prevalence of resistance to these alternative agents in some regions has raised concerns about the adequacy of current treatment protocols and the importance of antimicrobial stewardship [4].

Antimicrobial susceptibility testing (AST) has emerged as a critical tool in guiding treatment decisions, particularly in settings where resistance patterns are shifting. AST helps identify effective antibiotics for patients who cannot receive penicillin and aids in monitoring emerging resistance trends, which can inform clinical practice and public health policies. While susceptibility testing is not routinely performed for GAS due to its universal susceptibility to penicillin, it becomes essential in specific clinical scenarios:

1. **Treatment failure or recurrent infections**: When empirical therapy is unsuccessful, AST can identify resistance patterns and suggest alternative treatments.
2. **Penicillin-allergic patients**: For these individuals, AST helps guide the selection of alternative agents, such as macrolides, clindamycin, or cephalosporins.
3. **Epidemiological surveillance**: Tracking resistance trends is essential for understanding the spread of resistant strains and adjusting treatment guidelines accordingly [5,6].

Despite its clinical importance, susceptibility testing for GAS is complicated by the bacterium's unique resistance mechanisms and the variability in resistance rates across regions. For example, while penicillin resistance remains nonexistent, macrolide resistance has become a significant concern in parts of Asia, Europe, and North America. The primary mechanisms of macrolide resistance include ribosomal methylation (mediated by the **erm** genes) and efflux pumps (mediated by the **mef** genes) [7]. These mechanisms not only complicate treatment decisions but also underscore the importance of robust testing methodologies and regional surveillance.

The methodology for susceptibility testing includes traditional techniques such as disk diffusion and broth microdilution, as well as advanced molecular methods capable of detecting resistance genes directly. The choice of method depends on the clinical setting, available resources, and the need for rapid versus precise results. For example, while disk diffusion remains a cost-effective and widely used method in routine laboratories, molecular diagnostics offer faster detection of resistance genes but require specialized equipment and expertise [8].

This review aims to provide a comprehensive overview of susceptibility testing for pharyngeal GAS. It explores the methodologies, clinical applications, and global resistance trends while addressing the challenges and opportunities in this field. By synthesizing current evidence, this review seeks to highlight the importance of AST in optimizing the management of GAS pharyngitis, preventing complications, and promoting antimicrobial stewardship.

1. Importance of Susceptibility Testing in GAS Management

1.1 Clinical Implications

Susceptibility testing is particularly important for:

- Patients with recurrent pharyngitis or treatment failure.
- Individuals with penicillin allergies who require alternative therapies.
- Epidemiological studies monitoring antimicrobial resistance trends [4].

By identifying resistance patterns, susceptibility testing ensures the selection of the most effective antibiotics, minimizes the risk of treatment failure, and helps prevent the development of further resistance.

1.2 Global Burden of GAS Infections

GAS infections affect millions of people annually, with an estimated 616 million cases of pharyngitis worldwide each year [5]. Resistance patterns vary globally, with higher macrolide resistance reported in Asia and Southern Europe compared to Northern Europe and North America [6]. Surveillance data from programs like the World Health Organization (WHO) Global Antimicrobial Resistance and Use Surveillance System (GLASS) are essential for understanding regional resistance trends [7].

2. Susceptibility Testing Methods

2.1 Disk Diffusion Method

The Kirby-Bauer disk diffusion method is one of the most commonly used techniques for susceptibility testing in routine clinical laboratories. Antibiotic-impregnated disks are placed on an agar plate inoculated with the GAS isolate. After incubation, the zone of inhibition is measured and interpreted based on standardized guidelines (e.g., CLSI or EUCAST) [8].

- **Advantages**:

Cost-effective and easy to perform.

- **Limitations**:

Provides qualitative results (susceptible, intermediate, resistant) rather than precise MIC values.

2.2 Minimum Inhibitory Concentration (MIC) Testing

MIC testing provides a quantitative measure of an antibiotic's effectiveness by determining the lowest concentration required to inhibit bacterial growth.

- Methods:

Broth Microdilution: Serial dilutions of antibiotics in liquid media.

Etest Strips: A gradient of antibiotic concentrations impregnated on a plastic strip.

- **Advantages**:

More precise than disk diffusion.

- **Limitations**:

More labor-intensive and requires specialized equipment [9].

2.3 Automated Susceptibility Testing Systems

Automated systems like VITEK 2 and MicroScan offer standardized, rapid susceptibility testing.

- **Advantages**:

High throughput and integration with laboratory information systems.

- **Limitations**:

Expensive and not universally accessible in resource-limited settings [10].

2.4 Molecular Testing

Molecular methods detect specific resistance genes, such as **erm** (ribosomal methylation leading to macrolide resistance) and **mef** (macrolide efflux).

- **Advantages**:

Direct identification of resistance mechanisms without requiring bacterial culture.

- **Limitations**:

Limited availability and high cost [11].

3. Antimicrobial Resistance in GAS

3.1 Beta-Lactam Susceptibility

GAS remains universally susceptible to penicillin and amoxicillin, making these drugs the first-line treatment for pharyngitis. However, cases of tolerance, characterized by reduced bactericidal activity without full resistance, have been reported, raising concerns about treatment efficacy in certain scenarios [12].

3.2 Macrolide Resistance

Macrolide resistance rates vary widely, with some regions reporting rates exceeding 30% [13].

- Mechanisms:

Target Modification: Methylation of the ribosomal binding site (mediated by the **erm** gene) prevents macrolide binding.

Efflux Pumps: Mediated by the **mef** gene, efflux pumps actively expel macrolides from bacterial cells [14].

- Implications:

High resistance rates necessitate caution when prescribing macrolides, particularly in areas with known resistance.

3.2 Clindamycin Resistance

Resistance to clindamycin is less common but may involve similar mechanisms as macrolide resistance. Inducible resistance, detected via the D-zone test, underscores the importance of testing even in isolates initially appearing susceptible [15].

3.3 Tetracycline Resistance

Resistance is mediated by the acquisition of tet(M) and tet(O) genes, although tetracyclines are not first-line agents for GAS pharyngitis.

4. Standardized Testing Guidelines

The Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) provide standardized protocols for susceptibility testing. Defined breakpoints for interpreting susceptibility results. Recommendations for quality control to ensure reproducibility and reliability [16].

5. Role of Surveillance in Resistance Monitoring

Surveillance programs such as GLASS and regional initiatives (e.g., the U.S. CDC's Active Bacterial Core Surveillance) track resistance patterns and guide empiric therapy decisions.

- Data from these programs reveal:

Regional differences in macrolide and clindamycin resistance rates. Emerging resistance trends that warrant changes in treatment guidelines [17].

6. Challenges in Susceptibility Testing

6.1 Laboratory Resource Limitations

Resource-constrained settings may lack access to advanced testing methods, leading to reliance on empirical therapy. Advocacy for affordable, point-of-care testing is essential.

6.2 Variability in Guidelines

Differences between CLSI and EUCAST breakpoints can result in discrepancies in susceptibility interpretations, complicating clinical decision-making [18].

6.3 Delayed Results

Traditional culture-based methods may take 48–72 hours, delaying treatment adjustments.

7. Future Directions

7.1 Rapid Diagnostic Tools

Molecular and point-of-care tests capable of detecting GAS and resistance markers in under an hour are under development.

7.2 Novel Therapies

Research into new antimicrobial agents, such as peptide-based therapies, aims to address resistance challenges and provide alternative treatment options.

7.3 Global Collaboration

Strengthening international surveillance networks is critical for tracking resistance trends and developing coordinated responses.

Conclusion

Susceptibility testing for pharyngeal Group A *Streptococcus pyogenes* is an essential component of antimicrobial stewardship and clinical decision-making. While penicillin and amoxicillin remain effective first-line agents, resistance to alternative antibiotics, particularly macrolides and clindamycin, highlights the importance of testing in specific clinical scenarios. Advances in testing methods, from automated systems to molecular diagnostics, offer new opportunities for timely and accurate resistance detection. By standardizing protocols, addressing global disparities in diagnostic capabilities, and investing in surveillance and novel therapies, healthcare systems can optimize the management of GAS infections and mitigate the impact of antimicrobial resistance.

References

Andrews JM. Determination of minimum inhibitory concentrations. *Journal of Antimicrobial Chemotherapy.*2001;48(Suppl 1):5-16. DOI: 10.1093/jac/48.suppl_1.5.

Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. *The Lancet Infectious Diseases.* 2005;5(11):685-694. DOI: 10.1016/S1473-3099(05)70267-X.

Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing. 30th Edition. CLSI Document M100. Wayne, PA; 2020.

Colman G, Efstratiou A, Tanner G, et al. The serotypes of Streptococcus pyogenes causing disease in England and Wales, 1980–1990. *Journal of Medical Microbiology.* 1993;39(3):165-178. DOI: 10.1099/00222615-39-3-165.

Davies HD, McGeer A, Schwartz B, et al. Invasive group A streptococcal infections in Ontario, Canada. *New England Journal of Medicine.* 1996;335(8):547-554. DOI: 10.1056/NEJM199608223350803.

Efstratiou A, Lamagni T. Epidemiology of Streptococcus pyogenes. *Infections Due to Streptococcus pyogenes: Clinical Spectrum, Pathogenesis, and Control.* Karger Publishers; 2016:1-27. DOI: 10.1159/000441374.

Farrell DJ, Biedenbach DJ, Jenkins SG, Jones RN. Effects of macrolide-lincosamide-streptogramin resistance mechanisms on the in vitro activities of newer and traditional agents tested against Streptococcus pyogenes. *Antimicrobial Agents and Chemotherapy.* 2005;49(2):798-800. DOI: 10.1128/AAC.49.2.798-800.2005.

Kaplan EL, Johnson DR. Antistreptococcal humoral responses in children: Persistence of IgG antibodies after clinical infection and implications for susceptibility testing. *The Pediatric Infectious Disease Journal.*2001;20(10):1010-1016. DOI: 10.1097/00006454-200110000-00018.

Kim S, Caparon MG. Streptococcus pyogenes gains resistance to clindamycin through erm(B)-mediated ribosomal methylation. *Journal of Bacteriology.* 2010;192(16):4257-4263. DOI: 10.1128/JB.00484-10.

Murray PR, Baron EJ, Jorgensen JH, Landry ML, Pfaller MA. Manual of Clinical Microbiology. 9th Edition. ASM Press; 2007.

Richter SS, Heilmann KP, Beekmann SE, et al. Macrolide-resistant Streptococcus pyogenes in the United States, 2002–2003. *Clinical Infectious Diseases.* 2005;41(5):599-608. DOI: 10.1086/432005.

Seppälä H, Klaukka T, Vuopio-Varkila J, et al. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in Group A Streptococci in Finland. *The New England Journal of Medicine.*1997;337(7):441-446. DOI: 10.1056/NEJM199708143370701.

Shaikh N, Leonard E, Martin JM. Prevalence of streptococcal pharyngitis and streptococcal carriage in children: A meta-analysis. *Pediatrics.* 2010;126(3):e557-e564. DOI: 10.1542/peds.2009-2648.

Shulman ST, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update. *Clinical Infectious Diseases.* 2012;55(10):e86-e102. DOI: 10.1093/cid/cis629.

Steer AC, Lamagni T, Curtis N, Carapetis JR. Global mortality of group A streptococcus. *Clinical Infectious Diseases.* 2012;55(5):652-653. DOI: 10.1093/cid/cis430.

Woodbury RL, Klammer KA, Xiong Y, et al. Macrolide resistance in Streptococcus pyogenes: Detection of erm(A), erm(B), and mef(A) by real-time multiplex PCR. *Diagnostic Microbiology and Infectious Disease.* 2008;61(2):171-176. DOI: 10.1016/j.diagmicrobio.2007.12.012.

World Health Organization (WHO). Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report. Geneva: WHO; 2020.

World Health Organization (WHO). WHO Guidelines for the Treatment of Streptococcal Pharyngitis. Geneva: WHO; 2021.