Mycoplasma pneumoniae: Atypical Pathogen in Community Acquired Pneumonia

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Abstract

Mycoplasma pneumoniae is a one of most common reasons of respiratory tract infections in both adolescents and children with severity ranged from moderate to high. Many facts in the previous years regarding infections were induced via this organism having extra pathogenic mechanisms. Clinically, resistance to macrolide has produced internationally and represents a treatment trouble. Antimicrobial sensitivity checking out techniques have been applied, and novel antibiotics which are effective towards M. pneumoniae are present processing development. That evaluate concentrates on the several trends occurring in the previous quite a few years which beautify the grasp of that microorganism, which is one of the smallest pathogenic bacteria; however, is of extreme medical significance.

Keywords: Mycoplasma pneumoniae, community acquired pneumonia, macrolide resistance, treatment

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INTRODUCTION

The class of Mollicutes has 200 known species. Sixteen of these species are of human source; others belong to creatures and plants. Four species have essential significance in human which are: *Mycoplasma pneumoniae* causing pneumonia and joint infection. *Mycoplasma hominis* now and again proceeds baby blues fever and uterine cylinder diseases. *Ureaplasma urealyticum* causes nongonococcal urethritis in males and is related with pulmonary ailment in low birth weight newborns. *Mycoplasma genitalium* is firmly identified with *M. pneumoniae* imputing with urogenital diseases. Different Mycoplasma are pathogenic to the respiratory, urogenital tracts and joints of people.1

*M. pneumoniae*, was first found in 19442 termed as the Eaton operator. The small specialist couldn't be developed on standard bacteriologic media. Along these lines, it was initially thought to be an infection culturing that agent on a suitable medium suggesting the nowadays taxonomic nomenclature3,4,5.

*M. pneumoniae* is a mellow illness and is one of the basic reasons for respiratory tract diseases. It is a significant reason for community acquired pneumonia (CAP) and atypical pneumonia which is liable for mortality among children and adults6. The *M. pneumoniae* disease may be asymptomatic. It may cause genuine pneumonitis, hemolytic iron deficiency or an assortment of conceivable skin injuries7. *M. pneumoniae* pneumonia (MPP) is generally termed “walking pneumonia” due to the assumed kind. *M. pneumoniae* infection general mortality is low, up to 30%, particularly amongst old people8. Side effects, pneumonia seriousness and research facility were comparable paying little heed to macrolide resistance9,10 which may progressively lead to troublesome treatment11.

*M. pneumoniae* is the smallest microorganisms which can live independently in the world self-replicating on laboratory media. It is a pathogen between the microorganism and the virus in the respiratory system12. It has a little diameter (length of 1-2 μm and width of 0.1-0.2 μm). So, light microscopy can't recognize mycoplasmas12,13 as the colonies diameter is below 100 μm14. Mycoplasmas size is 125-250 nm and its shape is pleomorphic due to the fact they lack an inflexible cell wall as a “unit membrane” of 3 layers that includes a sterol. So, serum or cholesterol producing sterol must be added to the medium and they grow on agar producing colony whose center is generally fixed underneath the agar. Mycoplasmas affect human cell membranes and can be inhibited by its specific antibody1. They are penicillin resistant as the mode of action of penicillin is through inhibiting cell wall synthesis lacked in our organism. However, they are susceptible to tetracycline or erythromycin. *M. pneumoniae* genome comprises of 687 genes. As a result of that little genetic material, the life form was constrained in the capacities and unfit to incorporate inflexible cell wall. Then again, sterols offer a support in the cell membrane. Therefore, these life forms are uncaring toward β-lactams, and are unstained by the gram staining strategy. *M. pneumoniae* reproduces by means of binary fission with well-organized chromosome method. A specific cell organelle, that is liable for cytadherence copies before cell division16-18.

Epidemiology

The infection rate might be high in case of close contact among children and young adults (50–90%), but with variable frequency of pneumonitis (3–30%)1. Roughly 25% of patients had *M. pneumoniae* extra pulmonary signs19. Pneumonia is a significant indication of *M. pneumoniae* disease, as *M. pneumoniae* represents 10-40% of CAP cases {acute contamination of respiratory parenchymal tissue that is procured from the community enveloping patients who have not been hospitalized and not presented to any human services system}. The revealed occurrence of irregular *M. pneumoniae* in adults varied from 4% to 8% of CAP which may raise during epidemics to 70%20,21 and in immunocompromised Egyptian infants represented 11.1%22. *M. pneumoniae* hospitalization rate within the adults in the USA is around 100,000 hospitalizations annually. MPP stays undiagnosed due to its assumed nature, absence of demonstrative tests with great affectability and particularity and different diseases that either exist together or emulate *M. pneumoniae*12. Japanese examinations have shown a relationship of *M. pneumoniae* diseases with atmosphere changes, particularly with raised environmental temperatures and dampness during summer months. One examination demonstrated that...
each raise of 1°C leads to 17% expansion in MPP patients and 1% raise in moisture leads to 4% expansion24.

During the mid of year 2000 in Japan, macrolide-resistant M. pneumoniae (MRMP) was first observed and then extended to North America and Asia12. The pattern of MRMP is practically 90% of strains in the far east24,25. In Europe, MRMP showed 1% in Slovenia, the Netherlands and 30% in Italy26,27. MRMP represents around 10% in Canada and the USA of M. pneumoniae infections28-30. Many investigations recommend that the high administration of macrolides might be answerable for MRMP26,27 as macrolides represent 30% of every oral antibiotics recommended in the nation34. Up till now CAP is viewed as an intense illness, as it is the eighth reason for death in the USA, prompting extraordinary number of yearly deaths among children, which may reach up to 60,000 deaths35. Recently, resistance to macrolides quickly increased around the world, mostly in East Asia that was first found in Asia36 and have expanded to China (90%-100%), Japan (87%) and Korea (84.6%)36-38. In Europe and North America, MRMP was, 26% in Italy, 19% in Scotland and 13% in the United States12,39.

Pathogenesis

M. pneumoniae cause CAP which is additionally called atypical pneumoniae or strolling pneumonia. This sort of pneumonia is viewed as atypical because of the way that the cells causing the disease are impervious to penicillin, the medication that is ordinarily used to treat pneumonia. Direct damage of epithelial cells or the human resistant reaction leads to the M. pneumoniae diseases pathogenicity40. Toxic molecules are released (i.e., CARDS [community-acquired respiratory distress syndrome] toxin which is a pertussis toxin-like protein) as a result of airways attachment of M. pneumoniae to surfaces of epithelial cells41.

Occurring of pathogenicity starts as the organism attaches to the tissue of the host. Then, M. pneumoniae digests glycerol releasing H₂O₂ and superoxide causing cilia and epithelial cells damage. The impacts of H₂O₂ on host cells as red blood cells, incorporate hemoglobin denaturation, lipids peroxidation, and inevitable cell death. The oxidation effect in the pulmonary epithelium causes cilia disintegration42-45. From several investigations, MRMP has been associated with a more slow decrease in bacterial count, persevering side effects, for example, pneumonia, long hospital stay duration and extra-pulmonary manifestations resulting in change of antibiotic46,47. Also, other studies have identified infections of M. pneumoniae with asthma, and evidence indicates that M. pneumoniae may induce a bronchial system Th2 immune response48.

Virulence Factors

The attachment of M. pneumoniae to epithelial cells is very important for pathogenicity. The requirement for cytadherence is to get admission to nutrients from the host immune response and would additionally develop escaping from the immune system of the host. M. pneumoniae is adhered to the surface of epithelial cells as a result of proteins alteration by surface sialic acid and sulfated glycolipids. Binding is essentially desired to cause our microorganism motility on host cell surfaces, a feature associated with cell growth and pervasion of infection49. The most significant characteristic destructiveness elements of M. pneumoniae incorporate cytadherence. P30 and P1 are the primary grapple proteins which empower binding and are attached to M. pneumoniae terminal polar organelle. Unfavorable results of MPP is an ADP-ribosyltransferase exotoxin termed CARDS poison. They are critical harmfulness impacts producing cells ciliostasis and vacuolation. Cytotoxicity results from CARDS poison is additionally leads to free radicals creation41,50.

Mode of transmission and susceptibility

Direct contact is the main mode of transmission of M. pneumoniae. Also, secretions from the nose and throat of the infected patients when they cough or sneeze transmit M. pneumoniae and infection requires prolonged close contact with an infected person51. Elderly over 65 years, children around 2 years, immunocompromised patients whose take immunosuppressive therapy, patients with socioeconomic status and overcrowding52 and patients with respiratory illnesses are risked to the disease21. Heavy smokers can reach up to 50 to 400%53. Old ages have less MRMP than kids and teenagers, depending on macrolides regular use54. However, majority is seen within elderly, so it is a cornerstone among velocity contrast on
sickness\textsuperscript{21}. Mycoplasma infection is most frequent in late summer as lengthy as 1-3 weeks\textsuperscript{39}.

**Clinical Manifestations**

Pneumonia triggered through *M. Pneumoniae* is a self-limited illness, causing direct harm of the lung airlines and inflammatory reaction\textsuperscript{56}. Patients having ordinary or slightly raised absolute leukocyte and neutrophil counts and low C-reactive protein degrees, have CAP without *M. pneumoniae* infection. However, patients having CAP with the organism have less leukocyte and neutrophil counts\textsuperscript{12,57}.

A dry cough evolves to a wet cough within 4 days in acute infection and unusual pneumonia is the essential symptom detected in patients. The delayed onset of pharyngitis, sinus obstruction, uncommon otitis media, and ultimately extended lower respiration participation of pneumonia with low-grade fever and respiratory insinuates are the characterizations of the syndrome. Three weeks or slightly less are the incubation period previous to symptom development\textsuperscript{38,59}. There can also be moderate leukocytosis, however the entire white blood count does no longer regularly exceed 15,000/µL. Pneumonia signs and symptoms may additionally require approval to the scientific institution as blood oxygen is decreased and breathing is increased. Computed tomography (CT) is the useful choice detecting opacification of breathing is increased. Computed tomography (CT) is the useful choice detecting opacification of the air-space, thickening of bronchovascular cells, nodular leakage, and linear opaqueness. However, images of MPP cannot differentiate between nodular leakage, and linear opaqueness. However, patients having CAP with the organism have less leukocyte and neutrophil counts\textsuperscript{12,57}.

Extrapulmonary Manifestations

Extrapulmonary manifestations are associated with MRMP than with macrolide-sensitive *M. pneumoniae*\textsuperscript{74} and may occur as a result of delayed effective treatment of *M. pneumoniae* either, it is macrolide resistant or sensitive\textsuperscript{75}. Also, extrapulmonary disorders can predict *M. pneumoniae* virus coinfection as Adenovirus infecting children less than 3 years\textsuperscript{76}. These manifestations include skin, nervous, musculoskeletal, renal, cardiovascular, digestive and hematological systems\textsuperscript{77}. As *M. pneumoniae* is able to penetrate the epithelial cell membrane of the respiratory system, as well as, spreading outside the respiratory system developing different manifestations\textsuperscript{78}. *M. pneumoniae* may cause autoimmune hemolytic anemia as a result of changing red blood cells (RBCs) membranes antigenicity producing autoantibody. Also, common antigens shared between glycolipids of *M. pneumoniae* membrane and the heart, brain and lung tissues, causes the extrapulmonary manifestations resulting in host immune response associated with T-lymphocyte function disturbance, leukocytosis and intravascular clotting\textsuperscript{79}. Extrapulmonary disorders are common in children and may include alteration of liver functions developing acute hepatitis\textsuperscript{80}. Also, may include dermatological manifestations such as vesicular rashes, Stevens-Johnson syndrome and erythematous maculopapular\textsuperscript{77,81}. The probability of extrapulmonary manifestations is increased
in case of young people having CAP\textsuperscript{55}. Out of 152 children having CAP, 44 (28.9\%) were \textit{M. pneumonia} positive, and out of these children, 10 (22.7\%) had mucocutaneous lesions\textsuperscript{82}. After 2-14 days of respiratory illness, CNS problems include, meningitis, encephalitis, Guillain–Barre syndrome and optic neuritis\textsuperscript{83}.

**Diagnosis**

Culture is now not used for activities analysis due to the fact it is laborious requiring unique enriched media with incubation duration up to 21 days. Therefore, bacterial cultures are generally time-consuming\textsuperscript{55}. Pleuropneumonia-like organisms (PPLO) stock containing tubes were vortexed, the swab was disposed of, the substance went through 0.45 mm channels and immunized in sterile PPLO stock and brooded under microaerophilic conditions (5–10\% CO\textsubscript{2}) at 37°C until indications of Mycoplasma development were watched. The development of Mycoplasma spp. is demonstrated by a shading change to yellow or orange, in light of corrosive maturation of glucose. At that point, when this shading changed, 500 mL of the stock medium was subcultured on PPLO agar plate and hatched inside about a month. Following 14 days of hatching, agar plates were watched utilizing a transformed magnifying lens, at 400 amplification for the perception of Mycoplasma provinces. Further biochemical portrayal was performed utilizing hemadsorption and hemolysis tests\textsuperscript{84}.

\textit{M. pneumonia} infections can be difficultly diagnosed due to the fact that mycoplasmas have not a cell wall so, can not be seen by Gram staining method. About 75\% of patients with MPP have a titer of cold agglutinin more than 1:64, the possibility of having \textit{M. pneumonia} infection was great\textsuperscript{12}. Some laboratory methods used to diagnose pneumonia include

- Standard polymerase chain reaction (PCR) is the technique of choice. \textit{M. pneumoniae} infection will become undetectable via PCR quicker than by way of serological evaluation as soon as antibiotic sensetivity is initiated\textsuperscript{12}.
- Chest radiography is the most important diagnostic imaging for CAP\textsuperscript{85}. The radiographic presentation of “atypical” pneumonia due to \textit{M. pneumoniae} is extraordinarily variable. Bilateral, diffuse interstitial infiltrates are common, pleural effusions can occur, however none of the radiographic findings related with \textit{M. pneumonia} CAP are specific\textsuperscript{86}.
- Estimating complete blood count (CBC), blood urea nitrogen, white blood cell count and serum creatinine to be utilized in seriousness scoring of the illness\textsuperscript{87}.
- Tests for specific antigens or antibodies blood culture. Blood culture is definitely not a routine indicative test of CAP cases and is prescribed to those with serious CAP\textsuperscript{85}.
- Serology (fourfold rise in IgG or IgM)\textsuperscript{1}.
- The utilization of various provocative biomarkers in the evaluation of patients with CAP like C-receptive protein (CRP) levels and procalcitonin, could foresee the bacterial etiology for CAP and help to keep away from the maltreatment of anti-microbial agents\textsuperscript{88}.
- A 4-fold change in titers after some time could be used for immunological determination (IgM titers rise before IgG antibodies). After16 days of manifestations, IgM measures increments with the span of indications, moving toward over 70\%. The prescient IgM estimation was about 80\%\textsuperscript{89}.

**Table 1.** \textit{M. pneumoniae} extrapulmonary diseases reported in children\textsuperscript{78}

| System          | Disease                                                                 |
|-----------------|-------------------------------------------------------------------------|
| Skin            | Unspecific rashes & Hives                                               |
| Neurologic      | Early-onset encephalitis/myelitis, Aseptic Meningitis.                  |
| Musculoskeletal | Arthritis, Myositis                                                     |
| renal digestive | Nephritis, Acute hepatitis, Acute pancreatitis                           |
| hematological   | Hemolytic anemia, Thrombocytopenia, Thrombosis                        |
| Cardiovascular  | Pericarditis, Myocarditis, Endocarditis                                 |

\textsuperscript{78}
Agar-and broth in vitro testing method was laborious. So, PCR methods could alternatively detect 23S rRNA region point mutations in respiratory samples as a macrolide resistance marker.

Normal reasons for CAP, notwithstanding *M. pneumoniae*, incorporate *Legionella pneumophila*, *Streptococcus pneumoniae*, *Chlamydia pneumoniae*, *flu AH1N1* and *Haemophilus influenzae*. Recently, SARS CoV2, SARS, *flu* infection (H1N1), avian influenza (H5N1), and MERS-CoV have developed to as the basic pathogens to cause serious pandemic CAP. So, the acknowledgment of the signs and side effects is significant. Sputum assessment, blood culture, and different tests dictate the causative living beings. Recently, an Egyptian examination has uncovered atypical bacterial disease and was analyzed in 13.3% of cases, at that point *Klebsiella pneumoniae* was 10.37%. *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* were 7.78%.

An examination in Zagazig college Pediatric clinic was performed to clarify the regular bacterial pathogens causing CAP among immunocompetent newborn children and preschool kids. Forty eight cases were examined. Infants having 1-72 months old gave indications of pneumonia as per world and health organization (WHO). All patients were exposed to the accompanying: data assortment, chest x-beam, blood culture, routine lab examination and sputum investigation. Immunofluorescent method detected (Ig) M antibodies against basic respiratory pathogens. By serological results, age changes can result

Treatment of *Mycoplasma pneumoniae* infection:

Penicillin, cephalosporins and vancomycin are insufficient. In the treatment of *M. pneumoniae*; antimicrobials against *M. pneumoniae* are bacteriostatic, not bactericidal and act on the ribosome of bacteria to hinder synthesis of protein such as, erythromycin. Those that inhibit DNA replication, for example, fluoroquinolones are exceptionally successful. Macrolides are generally viewed as the principal antimicrobials for *M. pneumoniae* CAP in kids on the grounds that the other options (for example fluoroquinolones) are not affirmed for use in the principal long periods of life. The utilization of macrolides with steroids has been suggested in serious instances of MPP.

Ketolides with macrolides explicit 23S rRNA nucleotides in the 50S subunit of ribosome, inhibiting synthesis of protein as they separate peptidyl-tRNA. Macrolides appear to adjust or direct the susceptible cell by hindering provocative cell chemotaxis, cytokine synthesis, responsive oxygen species creation and intracellular flagging pathways. Azithromycin is better than different macrolides, as it has more half-life than other macrolides, taking into account a shorter treatment duration. Also, fluoroquinolones are successful, having more MICs and consider as second line treatment for children. Patients with CAP should proceed with antimicrobial treatment for at least 5 days; 10 days is typically sufficient and antibiotic treatment could reach out to 14 days.

Advantages and Disadvantages of tetracyclines (TCs) and fluoroquinolones (FQs)

TCs and FQs advantages are lowering of manifestations with quick effect; however, they have numerous problems. Antibiotic medications are promptly bound to calcium saved in recently shaped bone or teeth in small kids. At the point when an antibiotic medication is given during pregnancy, it tends to be stored in the fetal teeth, prompting fluorescence, staining, and finish dysplasia. It can likewise be stored in bone, where it might cause deformation. If the medication is given to young age more than 8 years, comparable changes can result. Thus, these medications have not been suggested as first-line operators for patients under 18 years old.

A second-generation TC as doxycycline has less calcium binding, prompting decreased danger of staining of teeth finishing hypoplasia. Four mg/kg/day doxycycline was used for treatment for 10 days in 2-7 years asthmatic children. Four mg/kg/day was used for 7 days in 0.2-7.9 years kids having rhabdomyosarcoma (RMS) and 12.5 days treatment by 10 mg/kg/day in less than 8 years old kids having CNS disorders. However, staining of teeth was watched (2.8%) in grown-ups getting courses of doxycycline (100 mg twice day by day for a half year) for stomach aortic aneurysms. Jungle fever chemoprophylaxis by doxycycline could...
increase the danger of developing impervious bacteria to antimicrobials. Blanching with $H_2O_2$, crowns with high oral cleaning, staying away from daylight during treatment or vitamin C administration could prevent teeth staining. Often, unfavorable responses were developed with minocycline (3%-6% of grown-up patients). However, minocycline is alternative when doxycycline is unavailable.

Treatement of Macrolide Resistant M. pneumoniae (MRMP)

Conversely, macrolides show up clinical successful in certain patients having MRMP; macrolides could be used for treating 30% of MRMP. As M. pneumoniae infections are frequently self-limited, macrolides may lower the clinical side effects. Until now, the main elective medicines for MRMP are fluoroquinolones (FQs), TCs or fundamental steroids. Because of the association of MRMP and teeth harm emerging from antibiotic medication use, fluoroquinolone/tosufloxacin could be used as a second-line tranquilize in situations of MRMP during 2013-2015. However, M. pneumoniae also, showed resistance to fluoroquinolones according to in vitro studies.

Oral antimicrobial agents can’t be used for serious MRMP situations without serious consequences, minocycline can be utilized intravenously (4 mg/kg/day on the primary day, followed by 2 mg/kg at regular intervals for a limit of 100 mg). Doxycycline is suggested as a first line treatment when advantages surpass dangers. An another option, foundational corticosteroids have been utilized to decrease extra-or intrapulmonary signs. Prednisolone gives off an impression of being the best corticosteroid in treatment of CAP, because it initiate platelet in vitro non-gnomically. New antimicrobials, for example, lefamulin, solithromycin, naftifromycin, omadacycline and zoliflodacin are utilized to treat MRMP.

CONCLUSION

M. pneumoniae diseases are critical and influence all age groups, particularly the young adults and children. More studies are needed to build up accessible method for fast finding. There is no immunization to M. pneumonia and future research is needed for immunization advancement. Macrolide resistance was developed and might prompt delayed suitable antimicrobial treatment. Early determination of M. pneumoniae and the attention to macrolide resistance make early antimicrobial treatment conceivable and may improve clinical results.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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This article does not contain any studies with human participants or animals performed by any of the authors.

DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

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