GLUCOCORTICOID-INDUCED IMMUNOSUPPRESSION AND IMMUNOCOMPROMISED HOST PNEUMONIA

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ABSTRACT

Glucocorticoid is still a mainstay therapy in numerous diseases despite advances in novel chemotherapy and biologic immunomodulators. Estimated prevalence of glucocorticoid exposure is 1% in the general population. Glucocorticoid affect the immune system through various pathways, rendering those exposed to glucocorticoid immunocompromised. Studies have found that even at lower doses and short-term prescription, infection risk is increased in this population. Pneumonia is one of the leading causes of infection in the immunocompromised population, and based on the latest ATS/IDSA workshop report regarding immunocompromised-host pneumonia (ICHP), diagnosis and the etiologic workup differs compared to the community acquired pneumonia in immunocompetent patients. Approach to admission to inpatient care also differs due to the higher possibility of rapid deterioration of initially stable patients. Empirical treatment targets core respiratory pathogens but must be followed up to an attempt to determine causative pathogen according to clinical predisposition and imaging findings.

Keywords: immunocompromised host pneumonia, glucocorticoid

ABSTRAK

Glukokortikoid tetap menjadi opsi pengobatan penting untuk berbagai penyakit, meskipun telah ada kemajuan dalam kemoterapi dan terapi biologis. Sekitar 1% dari populasi umum diperkirakan terpapar glukokortikoid, yang mempengaruhi sistem kekebalan tubuh melalui berbagai jalur, sehingga meningkatkan risiko infeksi. Secara khusus, penelitian menunjukkan bahwa bahkan dosis rendah dan penggunaan jangka pendek dapat meningkatkan risiko infeksi. Pneumonia menjadi salah satu infeksi utama pada individu dengan imunitas menurun. Pedoman terbaru dari ATS/IDSA menekankan bahwa diagnosis dan pemeriksaan etiologis pneumonia pada pasien dengan imunitas menurun (ICHP) berbeda dari pneumonia yang didapat di masyarakat pada pasien yang imunokompeten. Keputusan untuk merawat inap pasien pada populasi tersebut juga sangat bergantung pada keputusan klinis karena memiliki risiko lebih tinggi untuk mengalami perburukan kondisi dengan cepat walau datang dengan klinis stabil. Pengobatan empiris biasanya menargetkan patogen pernapasan umum, tetapi penting untuk memperbaiki pendekatan ini berdasarkan temuan klinis dan pencitraan untuk secara efektif mengidentifikasi organisme penyebabnya.

Keywords: immunocompromised host pneumonia, glucocorticoid

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Introduction

Despite the increasing development of steroid-sparing modalities, glucocorticoid is still widely used as a first-line treatment for multiple ailments for its anti-inflammatory and immune-suppressing responses. Waljee et al found 21.1% of 1,548,945 non-elderly adults received at least one outpatient prescription for short term use of oral corticosteroid over a three-year period, defined as receiving oral corticosteroid for less than 30 days.[1] Indications for the prescriptions vary including upper respiratory tract infections, spinal conditions, and allergies.[1] For long term glucocorticoid use, the prevalence is estimated to be 1% in the general population and increases with age and among women.[2,3] Glucocorticoids provide relatively immediate relief for the symptoms associated with the disease, but adverse effects can cause major health concerns, such as infection due to its immune-suppressing qualities. Patients exposed to glucocorticoids were estimated to have a 50 – 60% higher risk for infection.[3] Long term use and cumulative dose of glucocorticoids were also associated with higher rate of infections such as pneumonia and increased risk of mortality.[4]

Pneumonia itself accounts for 75% of pulmonary complication amongst the immunocompromised with the highest burden of mortality, and is a long-recognized problem not well elucidated until recently.[5] With the development of novel biologic agents and cancer treatments, the mounting burden of immunocompromised host pneumonia is inevitable. Approximately 20% of community acquired pneumonia patients are immunocompromised.[6] A study by Ramirez et al found corticosteroid therapy accounted for 20% of the immunocompromised patients, the third highest after advanced stage cancer (53%) and cancer chemotherapy (23%).[7] The diagnosis of pneumonia in the immunocompromised host are challenging due to atypical presentations and a wider array of possible causative organisms, which includes opportunistic pathogens, compared to their immunocompetent counterparts.[5] Because of these challenges, The American Thoracic Society has recently attempted to bridge the knowledge gap in this population by publishing a workshop report regarding the matter formerly not addressed in the 2019 ATS/IDSA guideline for community acquired pneumonia.[8,9] Given the complexity of the diagnosis and management of this condition, this article is aimed to review the current evidence regarding the immunosuppression and infection risk of glucocorticoid use and immunocompromised host pneumonia.

Effect of Glucocorticoid on the Immune System

Glucocorticoids are steroid hormones that play an important role in regulating cellular functions such as cell metabolism, growth, and differentiation.[10] Glucocorticoids are widely used in the management of inflammation, autoimmune diseases, and cancer.[11] Glucocorticoids have effects on metabolic processes, energy regulation, stress response, and immunity.[10] The body produces cortisol in the range of 5-30 mg per day through regulation of the hypothalamic-pituitary-adrenal axis.[10] This hormone has a receptor called the glucocorticoid receptor (GR), which functions as an intracellular nuclear receptor responsible for the specific cellular and tissue effects of glucocorticoids.[11] The effects of glucocorticoid hormones also lead to negative feedback on the HPA axis.[10] The levels of glucocorticoid hormones are influenced by circadian rhythm, with the highest levels occurring around 9:00 AM and the lowest levels during midnight.[11]

Glucocorticoids inhibit the immune system's ability to recognize pathogens by disrupting the expression of receptors such as Toll-like receptors (TLRs), thus preventing an adequate immune response.[12,13] This is accompanied by the inhibition of post-pathogen detection signaling, resulting in a decrease in inflammatory mediators and antimicrobial peptides (cathelicidin, defensin, lysozyme) that play a role in innate

immunity. Glucocorticoids also inhibit the recruitment of leukocytes, especially polymorphonuclear leukocytes (PMNs), and their extravasation from vascular endothelium.[12,13] This leads to the accumulation of cells in tissues, along with the mobilization of immature PMNs and inhibition of apoptosis, causing neutrophilia.[12] However, their phagocytic activity is hindered.[12] The antiphagocytic effect is found at concentrations of 0.005-1 µg/ml, equivalent to plasma prednisolone levels that may occur with long-term routine use.[12]

Glucocorticoids also reduce the levels of eosinophils and basophils, as well as inhibit mast cell maturation and the production of cytokines, chemokines, arachidonic acid derivatives, and Fcϵ receptor expression.[12] Furthermore, the expression of major histocompatibility complex (MHC) class II decreases, leading to impaired T-helper (T_H) cell function, decreased production of IFN-γ and natural killer (NK) cells.[12,13] Glucocorticoids also have lympholytic effects that vary depending on the type of lymphocyte.[12,13] They induce apoptosis in T_H cells, particularly T_{H1} and cytotoxic T cells, and suppress activation, proliferation, and cytokine production, inhibiting T-cell-mediated responses. This can be seen in laboratorial exams as marked lymphopenia involving all lymphocyte subpopulations, including double positive T lymphocytes (CD4+ and CD8+).[13]

Glucocorticoids inhibit cytokine production by both T_{H1} and T_{H2} cells, thereby shifting immunity from cellular T_{H1}-mediated to humoral T_{H2}-mediated responses.[12,13] Glucocorticoids also affect B cells, although their impact is not as pronounced as on T cells.[10] They disrupt immunoglobulin (Ig) production, particularly IgG, while increasing IgE production. This places patients on long-term glucocorticoid therapy at risk of immunosuppression and susceptible to infections, including opportunistic infections as defined by the ATS.[9,12]

Glucocorticoid-induced Immunosuppression and Risk of Infection

Given the effect it has on the immune system, glucocorticoid has long been associated with increased risk of infection, including opportunistic infections (OI).[12] Duration, dose, dan intensity of glucocorticoid and additional use of other immunosuppressant agents have been linked with increased risk of infection.[12] Immunosuppressive dose of glucocorticoid is considered to be 2 mg/kg daily (for patients with body weight below 10 kg) or > 20 mg daily equivalent to prednisone (PEQ) for ≥ 14 days.[14] The ATS guideline considers chronic use of glucocorticoid of 20 mg PEQ for more than 2-4 weeks or lower doses (10 mg/d) for prolonged periods as a condition of immunocompromise.[9]

When it comes to duration, Waljee et al found the absolute risk for hospital admission due to sepsis during the five to 90 day period after initiation of short-term oral glucocorticoid (less than 30 days) was 0.05% (n = 170) compared to 0.02% in the non-users with incidence rate ratio of 5.30 (CI 95% 3.8 – 7.41); the incidence rate is significantly higher in patients with respiratory conditions.[1] Study by Fardet et al showed increased risk of infection in patients prescribed systemic glucocorticoid for over 15 days.[3] For the dose of glucocorticoid, most observational studies on rheumatoid arthritis and other inflammatory polyarthritis have shown the use of glucocorticoid of over 10 mg daily (PEQ) increase the risk of infections.[12,13] In systemic lupus erythematosus (SLE) patients with low disease activity, Abe et al found patients receiving glucocorticoid ranging from 5 – 7.5 mg PEQ, were at higher risk of infection with HR 6.8 (CI 95% 2.17 – 21.27) compared to those exposed to 0 – 2.5 mg PEQ.[15] Furthermore, some studies have found "low-dose" steroids may pose a hazard for patients; a dose as low as ≤ 5 mg daily PEQ were associated with increased hospitalized infections.[13,16] Widdifield et al found elderly patients with rheumatoid arthritis (RA) using less than 5 mg daily

PEQ had an increased risk of serious bacterial infection, with OR of 3.96 [95% CI 3.67, 4.27] and for those using >20 mg/day it was 7.57 (95% CI 6.87, 8.34).[12,17]

A population based cohort study by Fardet et al found the most frequent infections are lower respiratory tract infection and local candidiasis, especially during the first weeks of glucocorticoid exposure.[3] By the mechanism of which it affects the immune system, patients with chronic use of steroids have an increased risk for opportunistic infections including *Pneumocystis pneumonia*, invasive pulmonary aspergillosis, herpes zoster (HZ), and tuberculosis (TB), as well as typical causes of community acquired pneumonia (CAP).[6,9,13,18]

Immunocompromised Host Pneumonia

Immunocompromised host pneumonia (ICHP) is defined as an infectious pneumonia in an individual with a quantitative of functional defect in their immune defense system.[9] The diagnosis needs only a clinical suspicion of lung infection with or without compatible clinical signs and symptoms, but must have a radiographic evidence of new or worsening infiltrate.[9] Disruption of the immune defense system should be present during infection, as in severe sepsis, there may be a transient decrease in the immune system, which does not fall into the ICHP category.[9] Patients with malignancy but no longer have immunodeficiency conditions, such as no longer experiencing myelosuppression or no longer using immunosuppressants, or patients with solid organ malignancies undergoing local therapy, are not included in these criteria.[9] Furthermore, systemic conditions with metabolic effects that can affect the immune system are not considered conditions of decreased immunity but are comorbidities, such as diabetes mellitus and chronic liver disease, as well as structural lung disorders such as chronic lung disease, bronchiectasis, and chronic obstructive pulmonary disease (COPD).[9] Conditions categorized as immunocompromise in the report were cancer and hematopoietic cell transplant recipients, HIV, chronic immunosuppression and the use of novel biologics, solid organ transplant, and inborn errors of immunity.[9]

A study by Ramirez et al. on patients hospitalized for community-acquired pneumonia in Louisville found that 10% of patients had immunodeficiency.[7] Meanwhile, Di Pasquale et al. found that 18% of patients hospitalized for pneumonia had immunodeficiency conditions.[19] Additionally, data from Wu et al.'s research indicated that as many as 30% of patients admitted to the ICU with pneumonia had immunodeficiency conditions.[20] The difference in prevalence suggests that patients with decreased immunity are likely to have worse clinical presentation and a higher likelihood of ICU care.[20] This translates to higher mortality risk in immunocompromised patients, with a mortality rate of 26.1% at 7 days (vs. 13.1% in immunocompetent patients) and an ICU mortality rate of 49.6% (vs. 37.6% in immunocompetent patients with p = 0.027).[20] Meanwhile, a study by Ramirez et al. showed mortality rates in patients with decreased immunity vs. immunocompetent patients of 9% vs. 5% during hospitalization, 24% vs. 11% at 30 days post-discharge, 44% vs. 21% at 6 months, and 53% vs. 27% at 1 year.[7]

Diagnosis and Management of ICHP

The condition of immunocompromise lead to an increased risk of pneumonia due to typical organisms with more frequent, severe, prolonged, or recurrent manifestations compared to immunocompetent individuals.[9] This weakened immune condition also increases the risk of infection by uncommon or opportunistic pathogens.[9] However, identifying the etiological microorganism can be challenging. As mentioned before, the diagnosis of ICHP starts with the suspicion of pulmonary infection despite inconsistent signs and symptoms. The mnemonic DIRECT approach (Table 1) details the steps that must be taken in approaching suspicions of ICHP, established by Azoulay et al.[21]

Table 1. DIRECT approach[21,22]

D. Delay: time since respiratory symptoms onset, since antibiotic, antiviral, or antifungal prophylaxis or treatment, since transplantation, since the diagnosis of malignancy or inflammatory disease
I. Immune deficiency: knowledge of the nature of immune defects and ongoing antibiotic, antifungal, or antiviral prophylaxis will give information about missed opportunistic infections
R. Radiographic appearance: A chest radiograph will not only report the extent and the patterns of pulmonary infiltrates (consolidation, air bronchogram, nodules, interstitial pattern), but also presence and importance of pleural effusion, mediastinal mass, cardiomegaly, pericarditis, etc
E. Experience: the clinical experience of the ICU team and specialist consultants with this type of patients (treatment-related toxicity, viral reactivation, atypical form of diseases, graft-versus-host disease, cardiac involvement, etc.)
C. Clinical picture: the presence of shock is likely to be associated with bacterial infection, but may be seen in hemophagocytic lymphohistiocytosis, toxoplasmosis, adenoviral infections, HHV6 reactivations, or severe Sars-Cov-2 infection. Similarly, absence of fever or presence of tumoral syndrome (liver, spleen, and lymph nodes) will be considered as a possible orientation
CT scan provides a better description of the radiographic patterns and guides the need for non-invasive or invasive diagnostic tests strategy

Infectious causes in ICHP includes viral infection (cytomegalovirus, respiratory synctitial virus, adenovirus, parainfluenza virus, SARS-COV-2, herpes simplex virus, varicella zoster virus, human herpes 6 virus), fungal (invasive pulmonary aspergillosis, *Pneumocystis jirovecii*, *Cryptococcus neoformans*, and endemic mycosis), bacterial (gram positive, gram negative, *Nocardia*, mycobacteria), and protozoa or parasites (toxoplasma, *Strongyloides*, *Paragonimus*, geohelminths).[6,21,22]

CT-scan is a preferred method for diagnostic imaging of ICHP compared to plain chest x-ray.[22] Some radiologic markers found in CT-scan can help determine causative organism in ICHP.[22] The preferred quality of the CT Scan are slice thickness of < 1.5 mm of high resolution to detect interstitial patterns, a common pattern found in ICHP.[22] High resolution CT-scan (HRCT) is considered fundamental in diagnosis if the patient presents with severe manifestation in the first 24 hours or failure to respond to adequate antibiotic therapy after 72-96 hours, and high suspicion of invasive fungal infections (IFI).[22] Complete clinical context and underlying disease, as well as temporal relation to other risk factors must be put in consideration when interpreting the HRCT results; some non-infectious complications due to treatments are also frequent in the population.[22] Non-infectious differential diagnosis of respiratory failure in the immunocompromised include radiation, drug induced pulmonary toxicity, diffuse alveolar hemorrhage, pulmonary edema, and lung lesions cause by underlying diseases (e.g leukemic infiltrates, lymphangitic carcinomatosis, pulmonary vasculitis, graft vs host disease, etc).[22] Radiographic findings that commonly found in ICHP varies, ranging from nodes and masses, cavitation, ground glass attenuation, consolidation, or opacities, budding tree images, bronchial wall thickening, to pleural effusions and spontaneous pneumothorax.[21,22]

The ATS report on ICHP stated that the diagnosis of ICHP does not require detection of etiologic microorganism especially if no other probable alternative non-infectious diagnosis is present, but without foregoing the attempt to identify causative organism.[9] Therefore, adequate empirical management is mandatory.[9] The principle of treatment is that the core respiratory pathogens in the immunocompromised patients are the same as the immunocompetent, but attention

should also be given beyond the core pathogens commonly found in immunocompromised patients and which antimicrobial therapy is available.[6] Clinically, patients exposed to glucocorticoids are predisposed to infections by *Pseudomonas aeruginosa*, *Pneumocystis jirovecii, Staphylococcus aureus,* mycobacteria, *Aspergillus,* cytomegalovirus, varicella-zoster, herpes simplex, *Histoplasma capsulatum, Coccidioides, Cryptococcus neoformans, Nocardia, Legionella,* and *Strongyloides.*[6] Moreover, it is possible for the immunocompromised host to have more than one viral, bacterial, fungal, or parasitic agent.[22]

The decision for hospitalization require clinical judgement and low threshold of admission from clinicians because rapid deterioration of initially stable patients is possible.[9] Wider range of causative organism might also require parenteral agents.[9] The decision for outpatient management must be followed by close monitoring.[6] Microbiologic testing and bronchoalveolar lavage decision is derived individually for each case, putting into account local common pathogen, availability of tests, and the presence of risk factors of particular pathogens.[6]

Conclusion

The presence of pneumonia in patients exposed glucocorticoid must alarm physicians on the possibility of an immunocompromised host pneumonia. Despite the description of immunosuppressive dose of glucocorticoid, short term low dose steroid can also increase the risk of infection in this population. Approach to diagnosis must also include pathogens other than common causative microorganisms. Plain chest x-ray can help identify involvement of extrapulmonary tissues such as pleural effusion or mediastinal mass, but CT-scan is a better modality to help decide advanced diagnostic approach. Microbiological examination is based on availability of the test of specific organisms and whether antimicrobial therapy is available. The threshold for inpatient admission must be lower because atypical symptoms and rapid deterioration is not uncommon.

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References:

1. Waljee AK, Rogers MAM, Lin P, Singal AG, Stein JD, Marks RM, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. BMJ. 2017;357:j1415.
2. Monge Chacón AG, Wang C, Waqar D, Syeda SA, Kumar R, Meghana DR. Long-Term Usage of Oral Glucocorticoids Leading to Adrenal Insufficiency: A Comprehensive Review of the Literature. Cureus. 2023;15(5).
3. Fardet L, Petersen I, Nazareth I. Common Infections in Patients Prescribed Systemic Glucocorticoids in Primary Care: A Population-Based Cohort Study. 2016 [cited 2024 Feb 1]; Available from: http://www.csdmruk.imshealth.com/index.
4. Guo HJ, Ye YL, Cao R, Liu ZH, He Q. Association between the cumulative dose of glucocorticoids before the development of pneumonia and death in patients receiving long-term glucocorticoids: a secondary analysis based on a Chinese cohort study. Front Med. 2023;10(July).
5. Peck KR, Kim TJ, Lee MA, Lee KS, Han J. Pneumonia in immunocompromised patients: updates in clinical and imaging

features. Precis Futur Med. 2018;2(3):95–108.
6. Ramirez JA, Musher DM, Evans SE, Dela Cruz C, Crothers KA, Hage CA, et al. Treatment of Community-Acquired Pneumonia in Immunocompromised Adults: A Consensus Statement Regarding Initial Strategies. Chest [Internet]. 2020;158(5):1896–911. Available from: https://doi.org/10.1016/j.chest.2020.05.598
7. Ramirez JA, Chandler TR, Furmanek SP, Carrico R, Wilde AM, Sheikh D, et al. Community-Acquired Pneumonia in the Immunocompromised Host: Epidemiology and Outcomes. Open Forum Infect Dis [Internet]. 2023;10(11):1–9. Available from: https://doi.org/10.1093/ofid/ofad565
8. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia. Am J Respir Crit Care Med. 2019;200(7):E45–67.
9. Cheng GS, Crothers K, Evans SE, Aliberti S, Bergeron A, Boeckh M, et al. Immunocompromised Host Pneumonia: Definitions and Diagnostic Criteria An Official American Thoracic Society Workshop Report. Ann Am Thorac Soc. 2023;20(3):341–53.
10. Strehl C, Ehlers L, Gaber T, Buttgereit F. Glucocorticoids-All-Rounders Tackling the Versatile Players of the Immune System. Front Immunol. 2019;10(July):1744.
11. Timmermans S, Souffriau J, Libert C. A general introduction to glucocorticoid biology. Front Immunol. 2019;10(JULY).
12. Chastain DB, Spradlin M, Ahmad H, Henao-martínez AF. Unintended Consequences : Risk of Opportunistic Infections Associated With Long-term Glucocorticoid Therapies in Adults. 2023;(1):1–20.
13. Youssef J, Novosad S, Winthorp K. Infection Risk and Safety of Corticosteroid Use. Rheum Dis Clin North Am. 2016;42(1):157–76.
14. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58(3).
15. Abe K, Ishikawa Y, Kita Y, Yajima N, Inoue E, Sada K ei, et al. Association of low-dose glucocorticoid use and infection occurrence in systemic lupus erythematosus patients: a prospective cohort study. Arthritis Res Ther [Internet]. 2022;24(1):1–8. Available from: https://doi.org/10.1186/s13075-022-02869-9
16. George MD, Baker JF, Winthrop K, Hsu JY, Wu Q, Chen L, et al. Risk for Serious Infection With Low-Dose Glucocorticoids in Patients With Rheumatoid Arthritis A Cohort Study Analysis and interpretation of the data: M Critical revision of the article for important intellectual content: M HHS Public Access. Ann Intern Med [Internet]. 2020 [cited 2024 Feb 1];173(11):870–8. Available from: www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M20-1594.
17. Widdifield J, Bernatsky S, Paterson JM, Gunraj N, Thorne JC, Pope J, et al. Serious infections in a population-based cohort of 86,039 seniors with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2013;65(3):353–61.
18. Yang SC, Lai YY, Huang MC, Tsai CS, Wang JL. Corticosteroid dose and the risk of opportunistic infection in a national systemic lupus erythematosus cohort. Lupus. 2018;27(11):1819–27.
19. Di Pasquale MF, Sotgiu G, Gramegna A, Radovanovic D, Terraneo S, Reyes LF, et al. Prevalence and etiology of community-acquired pneumonia in

immunocompromised patients. Clin Infect Dis. 2019;68(9):1482–93.
20. Wu X, Sun T, Cai Y, Zhai T, Liu Y, Gu S, et al. Clinical characteristics and outcomes of immunocompromised patients with severe community-acquired pneumonia: A single-center retrospective cohort study. Front Public Heal. 2023;11.
21. Azoulay E, Russell L, Van de Louw A, Metaxa V, Bauer P, Povoa P, et al. Diagnosis of severe respiratory infections in immunocompromised patients. Intensive Care Med [Internet]. 2020;46(2):298–314. Available from: https://doi.org/10.1007/s00134-019-05906-5
22. Lletí MS, Navalón MDC, Pitarch MT, García-Bustos V. Etiology, diagnosis, and management of pneumonia in immunosuppressed patients. Rev Esp Quimioter. 2022;35:89–96.
23. Li L, Hsu SH, Gu X, Jiang S, Shang L, Sun G, et al. Aetiology and prognostic risk factors of mortality in patients with pneumonia receiving glucocorticoids alone or glucocorticoids and other immunosuppressants: A retrospective cohort study. BMJ Open. 2020;10(10).
24. Yang L, He D, Huang D, Zhang Z, Liang Z. Development and Validation of Nomogram for Hospital Mortality in Immunocompromised Patients with Severe Pneumonia in Intensive Care Units: A Single-Center, Retrospective Cohort Study. Int J Gen Med. 2022;15(December 2021):451–63.
25. Müller-Plathe M, Osmanodja B, Barthel G, Budde K, Eckardt KU, Kolditz M, et al. Validation of risk scores for prediction of severe pneumonia in kidney transplant recipients hospitalized with community-acquired pneumonia. Infection [Internet]. 2023;(0123456789). Available from: https://doi.org/10.1007/s15010-023-02101-z