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Infectious complications in patients with lung cancer

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Abstract. – Infections remain a part of the natural course of cancer. During the course of their disease, patients with lung cancer frequently present with an infection that can ultimately be fatal. Pathogenesis of infectious syndromes is usually determined by the underlying disease, as well as, the iatrogenic manipulations that occur during its management. Hence, lung cancer infections include lower respiratory tract infections in the context of COPD, aspiration, obstruction and opportunistic infections due to immunosuppression. Moreover, treatment-related infectious syndromes including post operative pneumonia, febrile neutropenia and superimposed infection following radiation/chemotherapy toxicity is common. Importantly, diagnosis of infection in the febrile lung cancer patient is challenging and requires a high index of suspicion in order to distinguish from other causes of fever, including malignant disease and pulmonary embolism. Prompt initiation of treatment is pivotal to avoid increased mortality. Careful consideration of infection pathogenesis can predict most likely pathogens and guide antibiotic management, thus, ensuring most favourable outcome.

Key Words:
Lung cancer, Pneumonia, Infections in oncologic patients.

Introduction

Patients with lung cancer suffer frequent infections which not only thwart the effect of oncological treatment but also affect overall survival[1-4]. Fever remains the most constant and often the only indicator of infection. Pulmonary tract infections, that constitute the majority of infections in lung cancer patients, are hard to distinguish from other causes of fever, including malignant disease, drugs, allergic reactions or thromboembolic events. Specific microbiological diagnosis is barely established for pulmonary infections. The interpretation of sputum and bronchoalveolar lavage (BAL) samples is problematical because of the lack of clear distinction between colonization and infection. Histological demonstration of microorganisms in tissue biopsy remains the most reliable proof of invasive opportunistic infection, but is rarely available because of the risk of haemorrhagic complications. Hence, the management of a lung cancer patient with fever is challenging. Prompt initiation of treatment is pivotal to avoid increased mortality. In such an attempt, the constantly growing list of opportunistic agents should be taken into account in addition to the wide array of conventional – often-resistant microorganisms. This article aims to review the most common infectious syndromes that occur in patients with lung cancer.

Epidemiology and Pathogenesis

The course of lung cancer is mostly complicated by pulmonary infections (50-70% of cases)[1,2,5-7], bacteremia, ear-nose-throat and gastrointestinal tract infections[8-10] irrespective of lung tumour histology or disease extent[6,9]. Small cell lung carcinoma (SCLC) seems to be associated with highest risk of pulmonary infection[2,10], while in neutropenic patients gastrointestinal tract infections predominate, mainly due to mucosal damage following cytotoxic chemotherapy[11]. Advanced stages of lung cancer and age >70, have also been implicated in higher infection rates[2,10].

The risk of infection in cancer patients depends on (1) the integrity of host defense mechanisms, including anatomical barriers, cell-mediated/humoral immunity, and (2) the intensity of exposure to potentially pathogenic microorganisms. Damage to anatomical barriers is common after chemotherapy, radiation therapy, inflammation or invasive procedures e.g. indwelling catheters, surgery. The underlying malignancy itself or immunosuppressive therapeutic interventions i.e. chemotherapy, corticosteroids and radi-

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ation therapy are responsible for immune defects in such patients[12]. Patient's pre-morbid health and performance status, e.g. diabetes mellitus, chronic heart, liver or kidney disease represent additional risk factors. Last, in such patients, regular in-hospital stays lead to changes and colonization of endogenous microflora, which in combination with obstruction of natural passages by neoplasm, facilitate microorganism proliferation and result in increased morbidity and mortality[13,14].

Infectious Syndromes

Infections related to lung cancer occur in the background of COPD, bronchial obstruction due to tumour growth and extension along lymphatics, or are related to lung cancer treatment, including surgery, chemotherapy and radiation therapy.

Infections of the Lower Respiratory Tract: Pneumonia in the Background of Chronic Obstructive Pulmonary Disease (COPD)

Lung cancer patients often represent an invariable population with COPD and long history of cigarette smoking. In these individuals, mucociliary clearance is significantly impaired, while, bacterial colonization with *Streptococcus pneumoniae* or *Hemophilus influenzae* is common. As a result, acute tracheobronchitis preceding acute exacerbations of COPD and persistent community acquired pneumonia is common. Nonetheless, at the moment data on lung infection at the background of COPD can only be extrapolated from studies on otherwise healthy individuals, since information on lung cancer patients with infection on the side of healthy parenchyma currently lacks.

In this setting, *S. pneumoniae, Haemophilus influenzae, Legionella pneumophila*, *Staphylococcus aureus*, *Moraxella catarrhalis*, *Escherichia coli*, and *Pseudomonas aeruginosa* represent frequent pathogens[15,16]. *S. pneumoniae* was mostly observed at home or during the first 48 h after hospital admission. In contrast, *S. aureus*, *Enterobacter* and *Proteus* species were isolated when the hospital stay was > 48h[9]. These patients present with cough, dyspnea, sputum production and pleuritic chest pain.

In addition, patients with COPD are also at risk for tuberculous and non tuberculous mycobacterial infections, to the point that routine screening is recommended by some Authors[17,18]. Presentation of non tuberculous mycobacterial infections resembles tuberculosis with fever, weight loss, hemoptysis and progressive dyspnea, whereas the risk of extrapulmonary dissemination is high[17].

Radiographic findings include cavitary lesions, pulmonary nodules, bronchiectasis and infiltrates. Multilobar pneumonia is commonly accompanied by bacteremia without, however, bacteremia being an indicator of disease severity. Nevertheless, the yield of blood culture in severe pneumonia is higher allowing accurate pathogen identification; hence appropriate antibiotic selection[16].

The goal of therapy is to provide optimal coverage for *S. pneumoniae* and *L. pneumophila* since both can be potentially fatal. Intravenous combination of an extended spectrum cephalosporin with a macrolide in hospitalized patients is recommended. Alternatively, a fluoroquinolone with antipneumococcal activity can be given. Clinical improvement typically occurs after 48 to 72 hours. Duration of therapy and switch to oral antimicrobials should be individualized according to the infective organism(s) and overall condition of the patient[15,19].

Changing patterns of sensitivities can alter the recommended regimen, depending on the local setting. Reports of *S. pneumoniae* increasing resistance to penicillin, cephalosporins, macrolides, and fluoroquinolones have been noted[9,20]. Risk factors of drug resistant pneumococcal infections in lung cancer patients include hospitalization and cancer treatment causing immunosuppression[21]. Their impact on clinical outcomes though remains controversial[22,23]. Regarding all other pathogens, the majority of *H. influenzae*, *M. catarrhalis*, and *E. coli* strains involved in lung infections appear to be susceptible to a combination of amoxicillin and clavulanic[9,24]. *S. aureus* strains not susceptible to methicillin represent a minority but are reported to be sensitive to vancomycin[9].

Obstructive Pneumonia

Post obstructive pneumonia, necrotizing pneumonia (cavities <2 cm) and lung abscess (cavities >2 cm) are putative complications of lung cancer occurring in approximately 20% of patients[2]. Obstructive lesions favour a damming back of secretions into the alveoli, the dilated bronchi or in severe cases of destruction, into the lung parenchyma. Intrinsic and extrinsic obstruction of the bronchus can further result in

atelectasis and lung collapse. Subsequently, microorganism colonization can lead to proliferation and infection.

Bronchial obstruction is more common in squamous and small cell carcinomas than in adenocarcinoma and large cell carcinoma. Necrotizing pneumonia often develops distal to the obstruction resulting in loss of lung parenchyma and cavity formation. Approximately, 7.6% of patients with lung cancer developed obstructive pneumonia, 13.2% and 1.7% of which, involved proximal tumors and peripheral tumors respectively[25].

Organisms causing post obstructive pneumonia include oral anaerobes (*Bacteroides, Prevotella, Fusobacterium, Actinomyces, microaerophilic streptococci), S. pneumoniae, H. influenzae, S. aureus,* and *Enterobacteriaciae* especially in chronically ill or institutionalized patients[26]. However, in several cases of lung abscess specimens, no anaerobic growth has been observed[27,28]. *Pseudomonas* and methicillin resistant *S. aureus* (MRSA) are also of increased prevalence. The latter pathogens in combination with *Klebsiella pneumoniae* and advanced age are associated with poor prognosis[29]. Fungal pathogens especially *Aspergillus,* are occasionally isolated from bronchial aspirates and can invade locally or form a fungus ball in presence of cavities. In many cases, however, more than one pathogen can be isolated[30].

Bronchoscopy remains an essential tool in diagnosis of post obstructive pneumonia, because not only it can provide an adequate specimen but also delineates the contribution of tumor invasion. Beyond common regimens, antibiotic coverage should be taken against anaerobes. Potential therapeutic options include, but are not limited to, clindamycin monotherapy or in combination with other agents, a beta-lactam/beta-lactamase inhibitor, or a carbapenem. Aggressive surgical approach can be of use, especially in presence of obstruction and lack of adequate drainage, that resolution has not been achieved with antibiotic administration[29,31,32].

Aspiration Pneumonia

In lung cancer patients, tumor invasion of the vagus or recurrent laryngeal nerve can occur. Glottal incompetence in combination with ciliary dysfunction due to radiotherapy increases the likelihood of aspiration pneumonia[32,33]. Aspirated oropharyngeal secretions give rise to colonizing bacteria in the lung. Untreated aspiration pneumonia can lead to abscess formation, necrotizing pneumonia, and empyema. In patients with high risk of aspiration, diagnosis is suspected by radiographic evidence of infiltrates in the dependent lung segments i.e. posterior segments of the upper lobes, apical segments of the lower lobes. Infections are usually of a mixed aerobic and anaerobic etiology; hence, antimicrobial therapy is similar to that for post obstructive pneumonia. Care of minimizing the risk of aspiration e.g. keeping the patient upright following feeding, should also be taken.

Opportunistic Pulmonary Infections

Patients with lung cancer often take corticosteroids for various reasons, including management of COPD. As a result, suppressed cellular immunity due to chronic corticosteroid use favors opportunistic pathogens, including pathogens of the genus *Aspergillus* and *Pneumocystis jiroveci.*

The incidence of invasive aspergillosis ranges from 1% to 8% in patients with solid tumors[3,34]. Except for pulmonary symptoms, invasive pulmonary aspergillosis is characterized by a localized, nodular infiltrate. The differential diagnosis should include *Trichosporon*, *Fusarium*, and *Rhizopus.* Travel history or environmental exposures should also give suspicion of *H. capsulatum, H. immitis*, and *Cryptococcus neoformans*. Isolation of a fungal pathogen from the respiratory tract usually correlates with infection. However, diagnosis is established following microbiologic or histopathologic confirmation in biopsy specimens. Treatment of these patients with voriconazole is efficient and produces better responses and improved survival, with fewer side effects than conventional treatment with amphotericin B[35,36]. Secondary to initial treatment, oral formulations of voriconazole/itraconazole are a good choice in outpatient care. Patients with *Pneumocystis* pneumoniae (PCP) present with fever, nonproductive cough, tachypnea, and hypoxemia. The time course of symptoms can vary significantly, but, acute onset is more typical in cancer patients. Auscultation of the lungs may reveal fine rales or be unremarkable. Chest X ray typically shows diffuse interstitial infiltrates, although other patterns include normal appearance or lobar infiltrates. An elevated lactate dehydrogenase may be present. Demonstration of cysts or trophozoites in respiratory specimens, either via sputum induction or bronchoalveolar lavage establishes the diagnosis[37]. PCP treatment of

choice includes trimethoprim-sulfamethoxazole p.o. or i.v. especially in severely ill patients, but other regimens are also available[37,38].

Treatment-Related Infectious Syndromes

Multimodal management of cancer patients also contributes to opportunistic infections.

Post Operative Infection

Pulmonary resection is a curative option for patients with lung carcinoma presenting as localized disease.Infectious complications after pulmonary surgery include operative wound infection and post operative pneumonia[39].

Postoperative wound infections occur in 2.4%-5% cases[40-43]. They are usually caused by *S. aureus* including MRSA and coaugulase negative *Staphylococci*. Leakage of anastomotic sites can lead to bronchopleural fistula formation, pneumonia and empyema in 0.4%-5% of cases[40-43]. These infections are usually polymicrobial and consist of Gram negative bacilli, anaerobes, and *Candida spp*. in addition to *Staphylococci*. Chest tube drainage and sometimes fibrinolysis or decortications are needed.

Postoperative pneumonia represents a common complication following thoracic surgery, ranging from 2% to 25% in patients who underwent pulmonary resection[40-45]. Notably, bacterial colonization of the bronchial tree in patients with resectable lung cancer can reach as high as 41% of cases[46]. It has been shown that previous or intra operative colonization of the respiratory tract by potentially pathogenic micro-organisms acquired from the patient's oral cavity, pharynx and hypopharynx may increase the risk of post-operative infection[45,47,48]. However, other studies do not confirm correlation between colonization and post-operative pulmonary infection[46]. Risk factors for nosocomial pneumonia after lung resection also include hospital stay, duration of mechanical ventilation (especially if >7 days) previous antibiotic therapy, presence of potentially drug resistant pathogens (especially MRSA and *P. aeruginosa),* structural lung disease and prior steroid use[49-51]. Postoperative pneumonia finally develops from atelectasis, retention of secretions or it can be aggravated by postoperative pain, sedatives and analgesia, as well as, phrenic nerve injury. Post operative pneumonia is associated with high mortality, despite currently used antibiotic prophylaxis[52].

Gram negative bacilli colonizing the digestive tract and upper respiratory tract during the preoperative period are the primary pathogens. Most cases of pneumonia were observed in the early postoperative week, with pathogens like *H. influenzae* (41.7%), *S. pneumoniae* (25%) and other streptococci (12.5%), *Enterobacter* spp. (8.7%) and *Pseudomonas* spp. (25%)[49]. More than one pathogen is isolated in more than one third of patients[45]. In such cases, institution of antibiotics should also include antipseudomonal activity. If patients are at risk of MRSA, vancomycin can be added, with alternatives of linezolid or quinupristin/dalfopristin in case of allergy or intolerance[49].

Infections Related to Radiation/Chemotherapy

Treatment modalities represent a risk factor for infectious complication in lung cancer patients. Common protocols of thoracic radiotherapy have been shown to give rise to various types of toxicity, including pneumonitis, esophagitis, and other types of mucosal trauma, predisposing for infection[53,54]. Patients receiving chemotherapy are also at higher risk of developing neutropenia, especially if myelosuppressive agents are used[55].

Radiation Toxicity and Superinfection

In lung cancer patients treated with thoracic radiation, the tracheobronchial tree is the prominent site of infection[10]. In those patients, Gram-negative bacteria, such as *H. influenzae*, and *P. aeruginosa,* are the most commonly isolated pathogens (70%) while, Gram-positive bacteria (26%) and fungi (4%*)* are also reported[10]. However, differentiation between actual radiation pneumonitis and superimposed infection can be challenging. An abrupt onset is more indicative of an infection. Review of chest radiographs and CT scans at initiation of, during, and after therapy is important. Infection should be considered if the chest radiograph shows pulmonary opacities occurring prior to completion of therapy or outside of the radiation portal. Similarly, cavitations within an area of radiation fibrosis generally represent superimposed infection and appropriate diagnostic and therapeutic steps should be taken[56].

The prevalence of severe acute esophagitis in patients treated for lung cancer is 1.3% with standard radiotherapy alone and 6% to 14% with the addition of concurrent chemotherapy[57]. Mucosal injury is frequently accompanied by Candida superinfection, facilitated by the presence of diabetes mellitus and corticosteroids[58]. Esophagitis

may arise as an extension of oropharyngeal candidiasis, although the oesophagus can be the only site involved. Diagnosis is primarily clinical and prompt empiric antifungal therapy is essential. Upper endoscopy with brushing and biopsy is recommended to confirm the diagnosis and rule out infection due to potential reactivation of herpes simplex virus (HSV) or cytomegalovirus (CMV), as well as, radiation or reflux esophagitis[53,59]. For mild to moderate oropharyngeal thrush, topical nystatin or clotrimazole troches may be used. Oral or intravenous formulations of azoles may be initiated in more severe cases or those with esophageal involvement. Resistance may require use of intravenous amphotericin B or caspofungin[60]. Duration of therapy is 7-14 days for oropharyngeal candidiasis, to 21 days for esophagitis.

Febrile Neutropenia

Patients with lung cancer develop neutropenia and fever secondary to chemotherapy[61]. A particularly dramatic increase of serious infections[62,63] is observed at a granulocyte absolute count[62,63] of < 500 cells/mm^3. Eventually, up to 60% of patients with granulocytopenia develop a lung infiltrate at some time reflecting pulmonary infection[64], associated with a shorter survival time[65].

Selective antibiotic pressure has recently led to the emergence of resistant Gram-negative bacteria, as predominant pathogens in neutropenic patients[9,66-69] even though discrepancies with predominance of Gram positive migroorganisms have been reported, depending on the subgroup of lung cancer patients studied[68,70-72]. The major species of pathogenic bacteria isolated from sputum before chemotherapy are *S. aureus*, *S. pneumoniae*, *H. influenzae* and *K. pneumoniae*. Following therapy, *S. aureus* including MRSA, *K. pneumoniae*, *P. aeruginosa*, *E. cloacae*, and *Acinetobacter calcoaceticus* are observed; known to be frequently involved in hospital-acquired infections[65].

Febrile neutropenia (i.e. presence of fever ≥38.0°C over 1 hour and absolut neutrophil count <500/mcL) should be considered a medical emergency and immediate management is crucial[61]. Empirical treatment should be started even before the results of cultures are available, and antibiotics should be given in maximum appropriate therapeutic doses. Should the cultures yield a specific pathogen, then the regimen can be modified accordingly.

Depending on the institution, monotherapy or combination therapy for the treatment of fever and neutropenia is employed, with similar rates of success[73]. Appropriate choices for monotherapy include a cephalosporin or a carbapenem. Combination therapy for febrile, neutropenic patients typically consists of a beta-lactam with antipseudomonal activity plus an aminoglycoside for synergism[61]. If patients improve within 48 to 72 hours, a course of 10 to 14 days is recommended. In contrast, lack of clinical response within 48-72 hours of empiric antibiotic therapy should prompt re-assessment. Therapy should be modified if there is concern about resistant organisms that may not be covered by the initial antimicrobial regimen or if less common etiologic agents are suspected.

Not all febrile neutropenic patients are at same risk for life threatening complications or death[74]. Good patient condition at presentation, absence of hypotension, outpatient status, absence of dehydration and age < 60, fall into a "low-risk" class of patients[75,76]. Importantly, lung cancer, as a solid tumour is also associated with good prognosis in febrile neutropenic cancer patients[68,75]. However, so is absence of chronic obstructive pulmonary disease, which in lung cancer patients is relatively common. Hence, complicating prognostic value. This "low-risk" subgroup of neutropenic patients may benefit from early discharge and outpatient treatment, avoiding further risk of nosocomial infection, improving the quality of life and reducing the cost[77]. Nevertheless, patients classified as low risk are still prone to serious and rapid alterations in their medical situation and close observation is essential.

Management of Febrile Lung Cancer Patient Diagnostic Approach

Infection in patients with lung cancer represents a diagnostic enigma given the inability of immunocompromised hosts to mount an adequate inflammatory response. The classic signs and symptoms of infection, other than fever, may be minimal or absent, especially in neutropenic patients[78]. Pulmonary infections constitute the majority of infectious incidents in lung cancer patients and should be primarily suspected. The clinical picture is atypical or nonspecific, involving dyspnoea and cough, with variable degree of hypoxemia. Radiological abnormalities especially in neutropenic patients can be ambiguous, including infectious lobar infiltrate, atelectasis, or pleural effusion. Notably, 25-50% of infiltrates are not

caused by infection in such patients[79], reflecting primary or metastatic sites of cancer, thromboembolic/haemorrhagic events, drug/radiation induced pneumonitis or even pulmonary oedema due to therapy induced congestive cardiac failure[79,80]. More than one third of granulocytopenic patients do not even have rales or any signs of consolidation[81]. Early CT is mandatory upon suspicion, since it can reveal a lung lesion not seen on radiography in 50% of individuals[82]. Nevertheless, findings can be both typical (e.g. an air-crescent sign suggestive of invasive lung aspergillosis), as well as, nonspecific (e.g. ground-glass opacities or diffuse nodular lesions suggestive of pneumonia caused by *P. jirovecii*, *Mycobacterium tuberculosis*, viruses, fungi, or interstitial lung inflammation by the underlying malignant disease)[83]. Sputum is seldom produced[84] and even when stained is not reliable[85]. Performance of bronchoscopy and BAL (unless contraindicated) and subsequent serological and molecular testing of specimen, are pivotal for establishment of the diagnosis[34,86,87]. US-guided transthoracic needle aspiration of cavitating lung tumours with suspected infection has also been proposed[88] and represents a direct and reliable way to obtain uncontaminated material for bacterial culture, avoiding complications of bronchoscopic procedures. Even though of therapeutic importance[7], eventual microbiological documentation of specific pathogens is possible in 40-50% of established cases of infection[11,89]. Last, in febrile cases resistant to empiric treatment that establishment of a definitive diagnosis has failed; open-lung biopsy sampling is recommended[90]. Diagnosis must be reached as quickly as possible in patients who are immunosuppressed and lung infiltrates are identified. A delay of more than 5 days in identification of the cause of lung infiltrates increases the risk of death by more than three times[91].

Antibiotic Approach

Prompt initiation of empiric treatment is recommended in all lung cancer patients, presenting of fever on suspicion of infectious origin. Empirical therapy should be modulated based on the individual setting. The most probable pathogen should be presumed on the basis of (1) potential sites of infection, (2) the nature of the treatment as a risk factor for specific pathogen (3) the degree and duration of potential immunosuppression, (4) the predominant environmental pathogens and (5) resistance patterns at the hospital/community setting where the patient receives care[92].

Prophylactic administration of antimicrobial agents has shown some benefit, especially during initiation of chemotherapy. Such task aims at patient protection during a vulnerable period, such as during neutropenia and mucositis. Prophylactic administration of ciprofloxacin plus roxithromycin during standard chemotherapy for SCLC reduces the frequency of febrile leukopenia, the number of infections, and the use of therapeutic antibiotics and attributed hospitalizations by approximately 50%[93]. Prophylactic use of a 7 day scheme of levofloxacin has also reported significant benefit[94]. Currently, antibiotic prophylaxis is not recommended, since, side effects, susceptibility to enteric infections, and emergence of resistant endogenous organisms are of concern[61]. Nevertheless, the reduction in mortality and infection rates outweighs the detriments associated with antibiotic administration[95], even though impact appears to be higher in patients with hematologic malignancies. Perhaps prophylaxis, preferably with a fluoroquinolone where resistance permits, should be considered for use in lung cancer patients at a higher risk for infection i.e. patients with known colonization, receiving corticosteroids, during chemotherapy cycles, etc.

Supportive Approach – Granulocyte Colony Stimulating Factors

Granulocyte growth factors (GCSF or GMCSF) are commonly used as adjunctive therapy in lung cancer patients with neutropenia. Prophylactic administration of granulocyte colony stimulating factors decreases the risk of febrile neutropenia and infection especially in high risk patients[65,96-98] i.e. patients > 65 y/o, with poor performance status, pre-existing neutropenia, extensive prior chemotherapy, irradiation to a significant amount of bone marrow, a history of recurrent febrile neutropenia, and co-morbid conditions[99,100].

However, impact of prophylactic use of granulocyte growth factors in SCLC[101] or NSCLC[102] remains unclear. Several studies have identified the significantly shortened duration of neutropenia following chemotherapy in SCLC patients administered GCSF or GMCSF either to maintain or to increase the planned dose-intensity. Yet no effect on response or survival has been found[101]. In fact, a detrimental effect of cytokine administration was observed in limited-disease patients treated concomitantly by chemotherapy and radiotherapy and in extensive-disease patients treated with concentrated chemothera-

py[101,103,104]. Similarly, there is no evidence for a benefit in response rate and survival from the use of granulocyte growth factors as support of chemotherapy for locally advanced and metastatic NSCLC[102]. As rates of febrile neutropenia due to chemotherapy vary substantially, administration of CSFs should be currently restricted to guidelines[99]. In the palliative setting, if the patient has high risk of developing febrile neutropenia or a neutropenic event, the use of granulocyte growth factors is reasonable, but dose reduction or chemotherapy delay are the principal options. More pilot studies are currently in progress in order to identify patient population that could potentially benefit from CSFs, since; therapeutic schedules are different depending on extent of disease.

Conclusions

Improvements in cancer diagnostic and therapeutic modalities have resulted in increased flora colonization of lung cancer patients, thus increased risk of superimposed infection. This risk can significantly affect prognosis in those patients, especially in the common context of immunosuppresion. Clinicians treating lung cancer patients should maintain a high index of suspicion for infection and orient management toward rapid diagnosis and appropriate antimicrobial treatment. Since the use of adjuvant therapies has still not been optimized in lung cancer patients, hope for the future lies in the development and broad availability of more targeted anticancer treatment, which limits damage to the immune system and natural barriers, thus, preventing serious and life threatening infections.

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