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Review Article

Pathogen spectrum and management strategies for opportunistic infections in lung cancer in the immunotherapy era: recent advances from fungi to mycobacteria

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Abstract: Lung cancer is one of the most common cancers and the leading cause of cancer death worldwide. Opportunistic infections (OI) are increasingly recognized in this population due to disease-related immune dysfunction and treatment-induced immunosuppression. Compared with the chemotherapy era, the use of immune checkpoint inhibitors and targeted agents has shifted the OI profile. Pneumocystis jirovecii pneumonia (PJP) and invasive pulmonary aspergillosis (IPA) are reported more often in older adults and patients with lymphopenia, while tuberculosis (TB) and nontuberculous mycobacteria (NTM) cluster in those with structural lung disease (e.g., bronchiectasis, cavities) and prolonged immunosuppression. High-risk features include absolute lymphocyte count <500/μL, corticosteroids ≥20 mg prednisone-equivalent for ≥4 weeks, airway obstruction, prior TB, chronic obstructive pulmonary disease/interstitial lung disease (ILD), and recent broad-spectrum antibiotics. Diagnosis should integrate high-resolution computed tomography (HRCT) patterns (e.g., diffuse ground-glass for PJP; nodules with halo sign for IPA), microbiology [bronchoalveolar lavage fluid (BALF) culture/microscopy, galactomannan (GM)/β-D-glucan (BDG)], and metagenomic next-generation sequencing, interpreted against host factors and treatment timeline, while carefully distinguishing immune-related pneumonitis and TKI-associated ILD. Prophylaxis with TMP-SMX is recommended for high-risk patients; voriconazole (or isavuconazole) is first-line for IPA with attention to drug-drug interactions; TB/NTM regimens require coordination with anticancer therapy, especially where rifamycins interact with TKIs. Vaccination (influenza, pneumococcus, zoster) and antimicrobial stewardship are essential. Future work should validate risk scores prospectively and clarify microbiome-immunotherapy-infection relationships.

Keywords: Lung cancer, opportunistic infections, pneumocystis jirovecii, invasive aspergillosis, tuberculosis, nontuberculous mycobacteria, mNGS, immunotherapy, vaccination, antimicrobial stewardship

Introduction

Lung cancer is among the most common cancers worldwide and the leading cause of cancer death [1]. The disease reshapes host immunity and fosters an immunosuppressive tumor microenvironment that weakens antimicrobial defense. Chronic, tumor-related inflammation further activates suppressive immune pathways and favors persistent airway colonization [2]. Many patients also carry exposures or comorbid conditions, like smoking, chronic obstructive pulmonary disease (COPD), and interstitial lung disease (ILD) that impair the local airway barrier [3]. In combination with disruption of the pulmonary microbiome, these factors raise the risk of opportunistic infections (OI) [4].

Treatment has changed markedly in the last decade. Immune checkpoint inhibitors (ICIs), molecularly targeted agents, and anti-angiogenic drugs have improved survival but introduced new infectious risks [5]. During the COVID-19 era, reports noted higher infection signals in patients with lung cancer, with the combined effects of anticancer therapy and viral pneumonia amplifying susceptibility to

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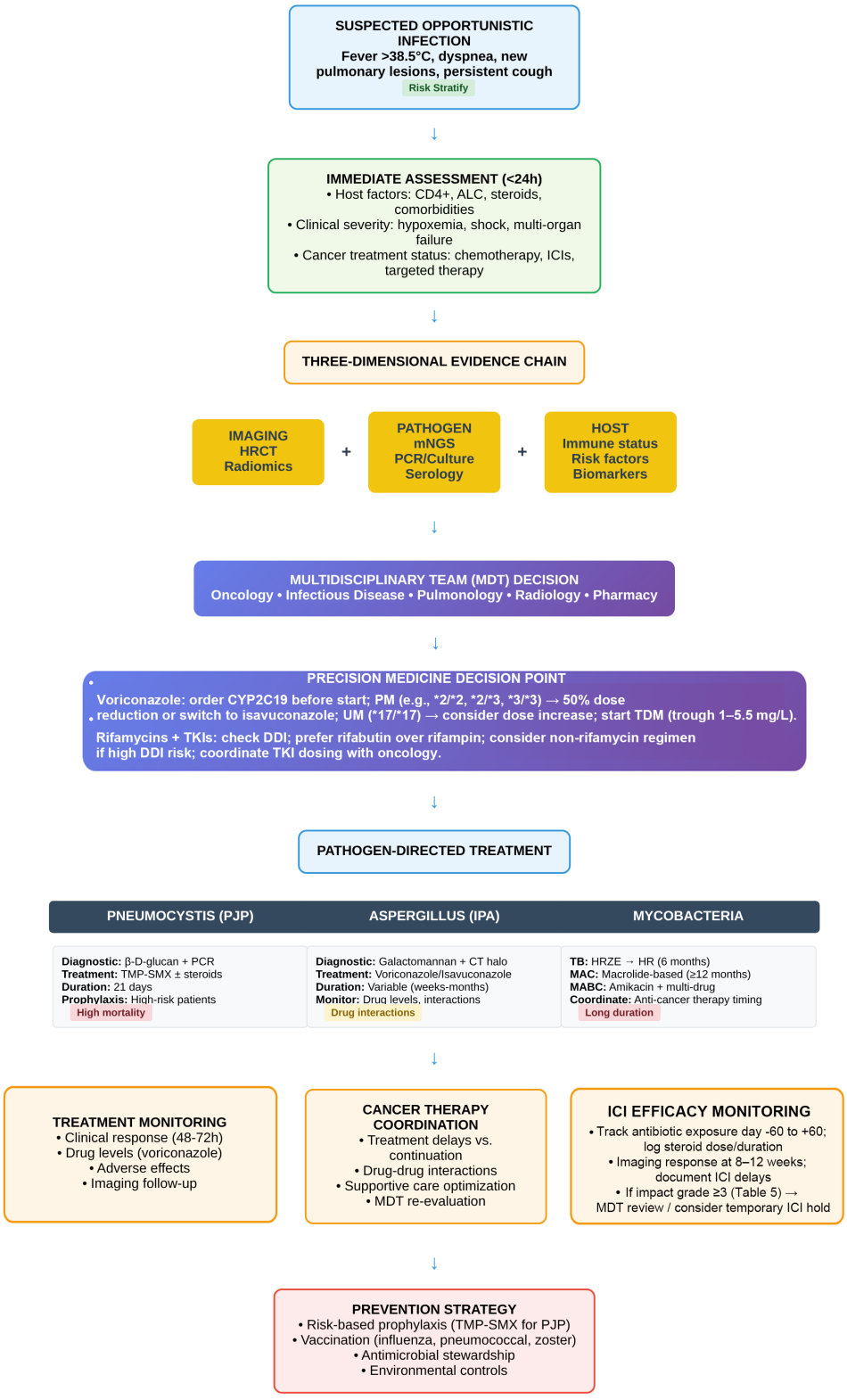
Clinical Decision Pathway for Opportunistic Infections in Lung Cancer Patients



⚡ Key Decision Points:

Emergency (≤4h): Severe hypoxemia, shock, rapid progression

Urgent (≤24h): High-risk features, immunosuppression

Routine (72h-108h): Stable, low-risk, outpatient management

Figure 1. Risk-stratified clinical pathway for managing opportunistic infections in lung cancer patients.

respiratory OI [6]. Some targeted agents may also perturb the host microbiome and increase infection risk over time [4]. Across selected cohorts, OI have been reported in roughly 10-30% of patients with lung cancer, with attributable mortality in those affected of 20-40%; beyond deaths, infections disrupt and delay anti-neoplastic treatment [7-9].

Clinical care still struggles with four recurring problems. First, early recognition is hard because symptoms and imaging overlap with tumor progression and treatment-related pneumonitis. Second, pathogen diagnosis is difficult. Cultures are frequently negative and newer molecular tests require careful interpretation. Third, therapy must balance antimicrobial efficacy with drug-drug interactions and overlapping toxicities. Fourth, prevention is inconsistent, as risk-stratified, evidence-based protocols are not uniformly applied. These gaps call for multidisciplinary approaches and a standardized framework that prioritizes prevention, timely detection, precise diagnosis, and individualized treatment.

To support translation into routine practice, we structure the evidence around an "imaging-pathogen-host" chain and distill it into a risk-stratified approach that clinicians can integrate into care. The key elements, who to screen and vaccinate, when to escalate diagnostics, and how to align prophylaxis and treatment with host and treatment-related risks, are summarized in **Figure 1** and **Tables 1-4**.

Epidemiology and pathogen spectrum

Epidemiological characteristics of fungal infections

Pneumocystis jirovecii pneumonia (PJP) has been increasingly reported in lung cancer cohorts. Among solid tumors, cumulative incidence estimates range from about 0.4% to 3.3%, with lung cancer contributing a large share of solid-tumor PJP cases [10, 11]. The association with ICI-based therapy remains debated. While early reports suggested higher PJP risk in ICI-treated patients, much of the excess risk appears driven by overall immunosuppressive burden (e.g., high-dose corticosteroids for immune-related adverse events, combination chemo-immunotherapy, baseline lymphopenia) rather than ICIs per se [11, 15]. In Indonesia, Zaini et al. found a 17.9% colonization rate of P. jirovecii in treatment-naive non-small cell lung cancer (NSCLC), underscoring region-specific epidemiology and the distinction between colonization and disease [12]. Unlike hematologic malignancies, non-HIV PJP in solid tumors often occurs with relatively preserved CD4+ T-cell counts, implicating multifactorial mechanisms including corticosteroids and respiratory microbiome dysbiosis [13]. Several Asia-Pacific cohorts have reported higher PJP incidence than many European/North American series; in mainland China, estimates in selected lung cancer populations range from roughly 2% to 6%, with reported mortality of 18% to 35% [10, 14]. In older adults (≥60 years), risk increases, likely reflecting immunosenescence, comorbidity, and polypharmacy. In a comparative cohort, ICI users with PJP showed higher 28-day mortality than non-ICI users (33.3% vs. 0; P=0.042), though sample sizes were limited [11]; by contrast, a nationwide analysis did not identify ICIs as an independent risk factor after adjustment [15].

Invasive pulmonary aspergillosis (IPA) is also increasingly recognized in lung cancer. Across surveillance studies, IPA incidence among solid tumors is approximately 0.5%-2.0%, with lung cancer accounting for the largest proportion of solid-tumor IPA cases (about 30%-50%) [13, 16]. Chemotherapy-induced neutropenia remains a principal risk factor, alongside corticosteroid exposure and structural lung disease. During severe respiratory viral infections, ICU cohorts have reported aspergillosis co-infection rates around 10%-20% for influenza and COVID-19, with higher mortality than in patients without aspergillosis; estimates vary by case definitions and diagnostic intensity [17]. Aspergillus fumigatus is predominant, followed by A. flavus, A. terreus, and A. niger; emerging azole resistance in A. fumigatus warrants attention [18]. Infections due to other molds and yeasts (e.g., Mucorales, Cryptococcus) are uncommon in lung cancer but may occur in specific high-risk settings (e.g., diabetes, prolonged high-dose steroids, certain regions) [19].

Table 1. Pneumocystis jirovecii Pneumonia (PJP) prevention and treatment regimens

Scenario	First-line Regimen	Dosage and Administration	Pharmacogenetic/DDI Considerations	Impact on ICI Efficacy (Grade)	Monitoring Parameters
Primary Prevention	TMP-SMX	TMP 160 mg + SMX 800 mg once daily or three times weekly orally	No significant pharmacogenetic variants; minimal DDI with TKIs/ICIs; avoid with methotrexate (↑toxicity)	Grade 1 (Minimal): Short-term prophylaxis, minimal microbiome disruption	CBC weekly × 4, then monthly; SCr, K+ (hyperkalemia risk); assess G6PD if hemolysis suspected
	Atovaquone	750 mg PO BID with food	CYP substrate (minor); requires adequate GI absorption; avoid with rifampin (↓75% levels)	Grade 1 (Minimal): Preferred alternative; negligible microbiome effect	LFTs baseline and week 2; ensure high-fat meal intake for absorption
	Dapsone	100 mg once daily	CRITICAL: G6PD testing mandatory (risk of severe hemolysis in deficiency); CYP2C19/3A4 substrate	Grade 1 (Minimal): No ICI interaction	G6PD before initiation; CBC q2 weeks × 8 weeks (monitor hemolysis, methemoglobinemia)
	Pentamidine aerosol	300 mg monthly via nebulizer	No major pharmacogenetics; local delivery limits systemic DDI	Grade 1 (Minimal): Minimal systemic exposure	Blood glucose (risk of dysglycemia), BP monitoring, renal function
Treatment-Mild to Moderate	TMP-SMX	TMP 15-20 mg/kg/d + SMX 75-100 mg/kg/d, divided 3-4 times, 21 days	Same as above; higher doses → ↑ DDI risk with warfarin, phenytoin	Grade 2 (Moderate): 21-day course may cause mild microbiome shift; generally well-tolerated	CBC q3 days × 1 week, then 2×/week; SCr, K+; consider folinic acid if cytopenia
Treatment-Severe	TMP-SMX + Corticosteroids	Prednisone 40 mg BID × 5 d → 40 mg QD × 5 d → 20 mg QD × 11 d	Steroid impact on ICI: Prolonged prednisone ≥40 mg may impair ICI efficacy if concurrent	Grade 3 (High): High-dose corticosteroids for severe PJP significantly impair ICI response; consider ICI hold during acute phase; balance survival benefit of steroids vs. ICI efficacy	Daily clinical assessment; ABG/SpO_2; CXR at day 7-10; glucose monitoring (steroid-induced hyperglycemia); taper steroids ASAP

Table 2. Invasive Pulmonary Aspergillosis (IPA) treatment strategies

Drug	Dosage and Administration	Pharmacogenetic Considerations	TKI/ICI Drug-Drug Interactions	Impact on ICI Efficacy (Grade)	Therapeutic Drug Monitoring (TDM)
Voriconazole	Loading: 6 mg/kg IV q12h × 2; Maintenance: 4 mg/kg IV q12h or 200 mg PO q12h	CYP2C19: PM (*2/*2, *3/*3) → ↑exposure, ↑toxicity (hepatic, visual, CNS); Consider 50% dose↓ or switch to isavuconazole. UM (*17/*17) → ↓exposure, treatment failure risk; may need dose↑	↓Imatinib (consider dosement nilotinib); ↓cyclophosphamide (active metabolite); QTc prolongation with TKIs (osimertinib, vandetanib); CYP3A4/2C19 interactions	Grade 2 (Moderate): Prolonged voriconazole (>4 weeks) may affect gut microbiome; hepatotoxicity can delay cancer therapy; prefer alternatives in ICI patients if feasible	Essential: Target trough 1-5.5 mg/L; check at day 5-7, then weekly; adjust dose if <1 or >5.5 mg/L; check with DDI changes
Isavuconazole	Loading: 200 mg IV q8h × 6 doses; Maintenance: 200 mg QD	Minimal pharmacogenetic variation; not significantly affected by CYP2C19 polymorphisms	Fewer interactions than voriconazole; safe with most TKIs; shortens QT (paradoxically beneficial if baseline; QTc); avoid with strong CYP3A4 inducers (rifampin)	Grade 1 (Minimal): Preferred for ICI-treated patients due to better tolerability profile and fewer DDIs; minimal microbiome impact	TDM not routinely required; consider in treatment failure or DDI scenarios
Posaconazole ER	300 mg PO q12h × 3 doses, then 300 mg QD	CYP3A4 substrate; no major pharmacogenetic predictors; absorption improved with extended-release formulation	↑Venetoclax (reduce venetoclax dose), aibrutinib (reduce dose 140 mg); monitor with midostaurin, other CYP3A4 substrates	Grade 2 (Moderate): GI absorption variability; monitor LFTs for hepatotoxicity (may delay chemotherapy); prolonged use affects microbiome	Target trough ≥1.0 mg/L (prophylaxis) or ≥1.5 mg/L (treatment); check at steady state (day 7-10)
Caspofungin	Loading: 70 mg IV, then 50 mg IV QD	No significant pharmacogenetic variants	Minimal DDI with TKIs/ICIs; no CYP interactions; rifampin may ocaspofungin levels (consider 70 mg daily if co-administered)	Grade 1 (Minimal): Ideal for combination with ICIs; no microbiome disruption; well-tolerated	TDM not routinely available; monitor clinical response and fungal biomarkers (GM)
Micafungin	100 mg IV QD	No major pharmacogenetic considerations	Similar to caspofungin; minimal TKI interactions; avoid with nifedipine (↑Ca-blocker levels)	Grade 1 (Minimal): Excellent for ICI patients; consider for empiric therapy in neutropenic fever	TDM not routinely required

Table 3. Tuberculosis and Nontuberculous Mycobacterial (NTM) treatment regimens

Infection Type	First-line Regimen	Duration	Pharmacogenetic/DDI Considerations	Impact on ICI Efficacy (Grade)	Cancer Therapy Coordination Strategy	Alternative Strategies for DDI Mitigation
Pulmonary TB	INH + RIF + EMB + PZA	6 months (2-month intensive, 4-month continuation)	Rifampin (RIF): Potent CYP3A4 inducer (no genotype needed); ↓80-90% dasatinib, ↓74% imatinib, ↓crizotinib, ↓osimertinib, ↓alectinib, ↓erlotinib. INH: NAT2 polymorphisms (slow acetylators → ↑toxicity risk).	Grade 3 (High): Rifampin DDI causes cancer therapy interruption/subtherapeutic levels → disease progression. However, TB control before/during ICI may enhance response in some cases (immune restoration). Net impact depends on cancer therapy type.	Option 1: Hold TKI during intensive phase (2 months), resume after TB control + switch to rifabutin. Option 2: Replace RIF with rifabutin (weaker CYP3A4 inducer; 450 mg daily) + increase TKI dose with TDM if available. Option 3: Non-rifamycin regimen (INH + EMB + PZA + fluoroquinolone, 9-12 months)-consult ID specialist.	For endemic TB regions: Baseline IGRA/TST before ICI initiation; treat LTBI with 3-month INH + rifapentine or 4-month RIF (coordinate with oncology for TKI-free window).
MDR-TB	Fluoroquinolone + Injectable + Bedaquiline/ Delamanid + 2nd-line oral agents	≥18 months	Bedaquiline: QTc prolongation (avoid with QT-prolonging TKIs: vandetanib, osimertinib at high doses). Fluoroquinolones: QTc risk, ↓seizure threshold with some chemo agents. No RIF → fewer DDI.	Grade 2-3 (Moderate-High): Long duration, multiple drugs, potential overlapping toxicities (hepatic, cardiac). Limited safety data with ICIs. ICI continuation requires case-by-case MDT decision.	Cardio-oncology consultation for QTc monitoring (baseline, week 2, 4, 8, then monthly); avoid other QT drugs; defer ICIs if Grade 3 + toxicity; prioritize TB cure over cancer therapy during intensive phase.	Consider shorter regimens (9-month BPaL or 6-month BPaLM) in eligible patients to minimize cancer therapy interruption; emerging data support efficacy.
MAC Infection	Azithromycin/ Clarithromycin + Rifabutin + Ethambutol	≥12 months (until culture-negative × 12 months)	Macrolides: CYP3A4 inhibitors (mild); ↑ibrutinib, ↑venetoclax. QTc prolongation risk with azithromycin. Rifabutin: Moderate CYP3A4 inducer; better TKI compatibility than RIF but still may ↓levels 30-50%.	Grade 2 (Moderate): Prolonged macrolide exposure may shift microbiome; generally compatible with ICIs. Monitor for GI toxicity (diarrhea) which may mimic irAE colitis.	TKI dose adjustment: May need 20-30% TKI dose increase with rifabutin (case reports with crizotinib, osimertinib). ICI: Generally safe to continue; monitor tumor response q8-12 weeks.	For severe/cavitary MAC: Add IV amikacin × 2-3 months initially; avoid concurrent cisplatin (nephrotoxicity); consider rifabutin dose reduction to 150 mg if TKI interaction concerns.
M. abscessus (MABC)	Amikacin + Cefoxitin + Clarithromycin	12-18 months	Amikacin: Nephrotoxicity, ototoxicity (monitor closely). Clarithromycin: CYP3A4 inhibitor effects. Genetic mutations in *erm* (41) affect clarithromycin susceptibility (test recommended).	Grade 1-2 (Minimal-Moderate): No major ICI interaction; main concern is overlapping nephro/ototoxicity with platinum-based chemo.	Avoid concurrent cisplatin/carboplatin during amikacin phase; coordinate with oncology for chemo schedule adjustment. ICI can continue with close toxicity monitoring.	Oral options: Tigecycline, linezolid (for later phase); clofazimine (emerging data). Monitor for myelosuppression (linezolid + chemo).
M. kansasii	INH + RIF + EMB	18-24 months (12 months after culture conversion)	Same RIF DDI concerns as TB (see above).	Grade 3 (High): If rifampin-based; similar TKI interaction profile.	Use rifabutin instead of RIF if concurrent TKI; extend duration to 24 months. Consider moxifloxacin-based regimen if rifamycin contraindicated.	Generally excellent treatment response; prioritize completing therapy even if requires TKI modification.

Table 4. Vaccination strategies

Vaccine Type	Recommended Population	Administration and Considerations	Interaction with Cancer Therapy	Impact on ICI Efficacy (Grade)
Inactivated Influenza Vaccine	All lung cancer patients annually	Avoid live attenuated vaccines; preferred timing: chemotherapy cycle intervals (7-14 days post-chemo for best response).	Safe during all cancer therapies; reduced immunogenicity during chemo (seroprotection ~60-70% vs. ~90% in healthy adults); consider high-dose formulation (Fluzone HD) for age ≥65 years	Grade 0 (Beneficial): Prevents influenza → reduces broad-spectrum antibiotic need → preserves microbiome → maintains ICI efficacy. Vaccination during ICI associated with improved outcomes in some cohorts.
Pneumococcal Vaccine (PCV13/PCV15/PCV20 + PPSV23)	Age ≥65 years or immunocompromised; consider in all lung cancer patients	Sequential strategy: PCV (13/15/20) first, then PPSV23 ≥8 weeks later (or ≥1 year if immunocompetent). Single-dose PCV20 may replace sequential strategy (emerging guideline).	Safe during chemotherapy, TKIs, ICIs; timing matters: administer PCV before chemotherapy if possible for optimal response; defer during severe neutropenia (ANC <500)	Grade 0 (Beneficial): Reduces invasive pneumococcal disease (IPD) incidence by ~26-fold in lung cancer vs. unvaccinated; prevents sepsis → fewer treatment interruptions and steroid use.
Recombinant Zoster Vaccine (RZV, Shingrix)	Age ≥50 years; age ≥19 years if immunocompromised	2-dose series (0, 2-6 months; can accelerate to 1-2 months if imminent high-level immunosuppression). Recombinant (not live) → safe during immunosuppression. Superior to live attenuated vaccine (Zostavax, which is contraindicated).	Safe during chemotherapy, ICIs, TKIs; transient reactogenicity (local pain, fever, myalgia) for 1-3 days is expected and acceptable; may temporarily mimic irAE but self-limited	Grade 0 (Beneficial): Prevents VZV reactivation (herpes zoster) → reduces need for acyclovir/corticosteroids; severe zoster can cause ICI interruption and secondary infections. RZV efficacy ~90% even in immunocompromised populations.
Other Live Vaccines (MMR, varicella, live zoster, BCG, yellow fever)	Contraindicated during active cancer treatment	Do not administer during chemotherapy, high-dose steroids (≥20 mg/d prednisone), or other significant immunosuppression; risk of vaccine-strain infection.	Absolute contraindication during immunosuppressive cancer therapy	Grade N/A (Contraindicated): Risk of disseminated vaccine-strain infection outweighs benefit; defer until immune recovery (typically ≥3 months post-chemotherapy, lymphocyte recovery, and off immunosuppressive doses of steroids).
COVID-19 Vaccines (mRNA or protein subunit preferred)	All lung cancer patients; boosters per CDC/local guidelines	Preferred types: mRNA (Pfizer, Moderna) or protein subunit (Novavax); avoid live attenuated (none currently available). Timing: any time during cancer therapy, but best response if 1-2 weeks before chemotherapy cycle.	Safe and recommended during all cancer therapies including ICIs, TKIs, chemotherapy; slightly reduced antibody titers during active chemotherapy but still protective	Grade 0 (Beneficial): COVID-19 causes severe illness/death in lung cancer patients; prevents infection → avoids prolonged antibiotics, high-dose steroids (for COVID pneumonitis), treatment delays. No negative impact on ICI efficacy.

Current epidemiological status of mycobacterial infections

Mycobacterium tuberculosis (TB) has dual relevance in lung cancer. Prior TB is associated with a higher subsequent risk of lung cancer, and TB may reactivate or newly occur during cancer treatment [20, 21]. Across multiple cohorts, prior TB has been linked to an adjusted increase in lung cancer risk, with hazard ratios (HR) around 1.7-3.5 after accounting for key confounders such as age, sex, and smoking [22, 23]. In a national Lithuanian cohort of 21,986 pulmonary TB survivors, 477 developed lung cancer during follow-up, corresponding to an approximately 3.5-fold higher risk versus the general population; the excess risk remained evident more than 20 years after TB diagnosis (about twofold). Prior TB was also associated with worse overall survival (OS) among patients with lung cancer (adjusted HR ≈ 2.4). During lung cancer therapy, TB typically presents as reactivation driven by the overall immunosuppressive burden, particularly prolonged systemic corticosteroids, cytotoxic chemotherapy, and thoracic radiotherapy, rather than any single agent effect [20, 21]. Mechanistically, TB promotes lung cancer development through chronic inflammation, fibrosis, immune exhaustion, and molecular signaling abnormalities [23]. Long-term granuloma formation and lung tissue remodeling lead to DNA damage and repair defects, activating multiple carcinogenic pathways [22, 24]. TB induces CD4+ and CD8+ T cell exhaustion; ICIs may partially reverse it, but cases of reactivation promotion have been reported [25].

Nontuberculous mycobacterial (NTM) infections in lung cancer patients warrant equal attention. A large Taiwanese cohort showed an 8-year all-cause mortality rate of 45.2% for NTM lung disease (NTM-LD), with M. kansasii infections showing the highest rate (59.2%, HR=2.20), followed by Mycobacterium abscessus complex (MABC) (HR=1.85) and M. avium complex (MAC) (HR=1.65) [26]. In Korean post-surgical lung cancer patients, the cumulative incidence of NTM pulmonary disease (NTM-PD) was approximately 2.8%, predominantly MAC infections. Among patients with concurrent lung cancer and NTM-LD diagnoses, M. avium accounted for 80.5%, with approximately half of cases having lung cancer and NTM-LD lesions in the same lobe, creating diagnostic and therapeutic challenges [27]. NTM infections commonly accompany COPD (21.1%), prior TB (18%), and bronchiectasis (32.3%), with immunosuppression (corticosteroid use rate 36.8%) representing an important background factor [28]. Immunotherapy may influence NTM disease course, with some cases showing NTM lesion deterioration after PD-1 inhibitor initiation, improving with combined antimicrobial therapy. Regarding pathogen co-infections, systematic reviews of NTM-Aspergillus co-infections show mortality rates as high as 43% globally, with imaging predominantly showing bronchiectasis (52.3%) and cavitation (40.8%), requiring simultaneous coverage of both pathogen types, with drug interactions being management challenges [28].

Overview of other important pathogens

Beyond fungi and mycobacteria, viral infections occupy important positions in lung cancer-associated OI [29]. Cytomegalovirus (CMV) represents one of the most common opportunistic viruses, capable of causing pneumonia, viremia, and even disseminated cutaneous infections in immunosuppressed populations [30]. Shen et al. [31] demonstrated CMV IgG positivity rates of 100% in surgically treated NSCLC patients, significantly higher than healthy controls. In advanced lung adenocarcinoma patients, particularly during epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) use and radiotherapy, CMV presents with rare disseminated cutaneous manifestations indicating poor prognosis [30]. Additionally, respiratory syncytial virus, parainfluenza viruses, and human metapneumovirus cause severe lower respiratory tract infections in immunosuppressed lung cancer patients [32]. SARS-CoV-2 has become a major threat to lung cancer patients since 2020, with multiple cohort comparisons showing significantly higher severe illness and mortality in lung cancer patients with COVID-19 compared to the general population [33, 34]. Regarding bacterial infections, gram-negative bacilli such as Pseudomonas aeruginosa, Klebsiella pneumoniae, and Escherichia coli are principal pathogens, commonly associated with mechanical ventilation, prolonged hospitalization, and broad-spectrum antibiotic use. Gram-positive bacteria including Staphylococcus aureus and En-

terococcus are more prevalent in central venous catheter-related infections [35, 36].

High-risk factors

Host-related risk factors

Host risk factors for OI in lung cancer are multifactorial, with overall immune competence being central [37]. Declines in T-cell immunity are strongly associated with PJP and CMV reactivation, whereas IPA is more closely linked to neutropenia, systemic corticosteroids, and structural lung disease rather than CD4 counts per se. In Indonesia, a 17.9% P. jirovecii colonization rate among treatment-naive NSCLC patients highlights the interplay of baseline should be distinguished from disease [12]. Persistent lymphopenia (e.g., absolute lymphocyte count [ALC] <1000/μL for >7 days, particularly at lower thresholds such as ALC <500/μL or CD4 <200/μL) signals elevated risk. High-dose corticosteroids (≥20 mg prednisone-equivalent for ≥4 weeks) and steroid pulses substantially increase PJP risk; certain monoclonal antibodies with lymphocyte-depleting effects (e.g., anti-CD20, alemtuzumab) also confer risk in oncology populations, although in lung cancer the excess risk is typically driven by steroids, chemotherapy, and baseline lymphopenia [38]. In multivariable analyses of ICI-treated lung cancer cohorts, COPD, asthma, lymphopenia, low CD4/CD8 ratios, and systemic corticosteroid exposure were independent predictors of serious infection [39]. In a nationwide ICI cohort, ICIs themselves were not an independent predictor of PJP after adjustment; risk was largely attributable to concomitant corticosteroids and lymphopenia [15]. Real-world data suggest serious infections cluster early after ICI initiation (e.g., within the first 60-90 days) and are predicted by prolonged/high-dose steroids for immune-related adverse events (irAEs) and pre-existing structural lung disease rather than direct ICI-induced lymphodepletion [39]. Large cohort analyses have also reported higher rates of active TB and latent tuberculosis infection (LTBI) conversion during ICI-based therapy compared with TKI-treated patients (e.g., aHR ≈ 6.29 for active TB; aHR ≈ 9.88 for LTBI conversion), though confounding by indication remains possible; prior TB history independently predicts reactivation (HR ≈ 3.59) [40].

Older adults (≥65 years) exhibit immunosenescence-thymic involution, expansion of memory T cells, and dysregulated inflammation, which increases susceptibility to OI [41]. The association between ICI use and infection risk remains debated. A nationwide study did not identify ICIs as an independent risk factor [15], whereas a comparative cohort observed higher short-term mortality among PJP cases occurring on ICIs versus non-ICI regimens, with small sample sizes limiting precision [11]. Comorbidities further modulate risk. Poorly controlled diabetes [e.g., hemoglobin A1c (HbA1c) >8%] increases susceptibility to bacterial and fungal infections [2]. COPD is linked to bacterial infections and predisposes to pulmonary aspergillosis; interstitial lung disease increases vulnerability across pathogens due to architectural distortion and local immune dysfunction [42]. Chronic kidney disease, hepatic dysfunction, and other organ impairment can compound immune dysregulation and affect anti-infective pharmacokinetics.

Anti-neoplastic treatment-related factors

Traditional cytotoxic chemotherapy remains the dominant iatrogenic driver of infection risk in lung cancer, via marrow suppression (neutropenia/lymphopenia) and mucosal barrier injury [43]. Risks vary by regimen and dose intensity and should be described by grade 3-4 neutropenia and, more importantly, febrile neutropenia (FN). In NSCLC, pemetrexed-platinum typically shows grade 3-4 neutropenia around 5-15% with FN about 1-3%, whereas paclitaxel-carboplatin reports roughly 10-30% grade 3-4 neutropenia with FN about 2-6%; gemcitabine-cisplatin can reach 20-40% with FN about 2-5% [44]. In SCLC, etoposide-platinum and topotecan-based regimens carry higher marrow toxicity, with grade 3-4 neutropenia around 30-60% and FN about 5-10% in trial cohorts [45, 46]. Bevacizumab is not myelosuppressive; adding it to paclitaxel/carboplatin does not consistently increase neutropenia beyond the backbone regimen, and reported grade 3-4 neutropenia usually remains below ~30-40% depending on schedule and patient selection [45, 46]. Primary G-CSF prophylaxis is recommended for regimens with expected FN risk ≥20%, and may be considered at 10-20% when host risk factors are present.

Radiotherapy's immune system impact demonstrates dose and site dependence. When chest radiotherapy doses exceed 40 Gy, obvious local immune function impairment shows, with radiation pneumonitis incidence of 15-30%, requiring differentiation from infectious pneumonia [47]. Whole brain radiotherapy can cause blood-brain barrier disruption, increasing intracranial infection risk. Concurrent chemoradiotherapy reveals synergistic enhancement of immunosuppressive effects, with severe infection incidence increasing 1.5-2 fold compared to chemotherapy alone [48]. McAleese et al. [49] found in large-scale lung cancer patients undergoing radical radiotherapy that those receiving high-dose corticosteroids and chest irradiation had significantly elevated risk of PJP-related mortality.

ICIs do not cause cytotoxic lymphodepletion. Early infections observed after ICI initiation often reflect concomitant immunosuppression used to manage irAEs and baseline structural lung disease [50, 51]. In lung cancer cohorts, serious infections tend to cluster within the first months of therapy and are predicted by prolonged/high-dose corticosteroids for irAEs and COPD/ILD, while ICIs per se are not an independent risk factor for PJP after adjustment [15, 39]. Prolonged high-dose steroids markedly increase OI risk and warrant consideration of PJP prophylaxis in selected patients (Management of toxicities from immunotherapy: European Society for Medical Oncology (ESMO) Clinical Practice Guideline). In parallel, TB reactivation has been reported more frequently under ICI-based therapy, supporting baseline TB screening and region-specific management [40].

Targeted therapy drugs have relatively smaller but significant immune impacts. EGFR-TKIs can cause ILD requiring differentiation from fungal pneumonia. Based on data from the Okayama Lung Cancer Study Group [52], approximately 35% of EGFR-mutated locally advanced NSCLC patients developed radiation-related pulmonary fibrosis after gefitinib plus chemoradiotherapy, suggesting the need for long-term clinical monitoring pulmonary complications associated with these regimens. Among anaplastic lymphoma kinase (ALK) inhibitors, crizotinib has immunomodulatory effects potentially affecting T cell function and increasing infection risks [53].

Healthcare-associated exposure factors

Inappropriate use of broad-spectrum antibiotics represents an essential risk factor for healthcare-associated OI. A retrospective cohort study from Tran et al. [54] suggests that NSCLC patients receiving broad-spectrum antibiotics within 30 days before or after ICI treatment had significantly shortened OS, potentially related to diminished immunotherapy response. Another research indicates [55] that high-dose or prolonged antimicrobial courses worsen immunosuppression and reduce antitumor immune responses, particularly when combined with corticosteroid treatment. Prophylactic antifungal use can reduce certain fungal infection risks but may also lead to resistant strain emergence and flora replacement phenomena. A systematic review reveals that for chemotherapy-treated lung cancer patients with pulmonary infections, empirical antifungal therapy reduces short-term infection mortality, but drug resistance and recurrence risks warrant long-term follow-up attention [56].

Invasive procedures and device use significantly increase infection risk. Central line-associated bloodstream infection (CLABSI) incidence ranges from approximately 0.8 per 1000 central line days in U.S. intensive care units to 4.1 per 1000 central line days internationally, with higher rates reported in low- and middle-income countries [57]. Endotracheal intubation and mechanical ventilation closely associate with ventilator-associated pneumonia, with the incidence of 10-15‰ ventilator-days [58]. While bronchoscopy represents standard lung cancer diagnostic procedures, iatrogenic infection risk increases when bronchoalveolar lavage is performed in immunosuppressed patients.

Surgical procedures represent another important infection exposure factor. Post-lung cancer resection pulmonary infection incidence is 15-25%, with 5-10% caused by opportunistic pathogens [59]. In a prospective study Li et al. [60], the incidence of surgical site infection was 13.47% after open thoracotomy lobectomy, with independent risk factors including operative time ≥180 minutes, American Society of Anesthesiologists (ASA) physical status 3/4, intraoperative blood loss 501-2000 mL, and respiratory failure.

Additionally, hospital environment exposure cannot be ignored. ICU stays >7 days, multiple ward transfers, and rooming with infected patients can increase hospital-acquired OI risk. Literature indicates [61] that fungal spores (such as Aspergillus) can rapidly colonize immunosuppressed host lungs under air exposure and inadequate room air filtration conditions, causing invasive fungal infections, such environmental exposure risks particularly require prevention in long-term hospitalized lung cancer patients.

Diagnostic strategies

Three-dimensional "imaging-pathogen-host" evidence chain

Modern diagnosis of lung cancer-associated OI has evolved from single evidence sources toward a three-dimensional "imaging-pathogen-host" evidence chain. Radiologically, IPA commonly presents as nodules or consolidation with halo signs, while PJP typically demostrates diffuse ground-glass opacities. Obmann et al. [62] found that immune status significantly influences imaging manifestations, with neutropenic patients more commonly showing consolidative IPA, while patients with partially preserved immune function more commonly present with peripheral nodules plus halo signs.

High-resolution computed tomography (HRCT) remains the preferred method for pulmonary infection diagnosis, with different pathogen infections presenting relatively characteristic radiological features. PJP typically manifests as bilateral diffuse ground-glass opacities with septal thickening showing "crazy-paving" patterns, but often presents as atypical focal lesions in lung cancer patients [63]. IPA frequently presents as nodular or mass lesions with or without cavitation, with "halo sign" and "crescent sign" having high specificity but appearing in only 20-30% of cases [64]. TB infections in immunosuppressed patients often show atypical imaging including diffuse miliary patterns or lobar consolidation [65]. Radiomics may aid CT-based differentiation in selected tasks by extracting subvisual texture features with machine learning [66, 67]. In small, predominantly single-center studies, PJP models have reported internal-validation sensitivity around 85-90% and specificity 80-85% for predefined binary comparisons, but head-to-head comparisons with thoracic radiologists, external validation, and calibration reporting are limited. Performance can degrade across scanners, protocols, and segmentation strategies; IBSI-compliant pipelines, harmonization, and prospective validation are needed before routine use.

Combining respiratory P. jirovecii PCR (preferably quantitative PCR on BAL with reported thresholds) with serum β-D-glucan improves rule-in performance; in [68], the positive predictive value was ~72%, which depends on pretest probability and specimen type. BDG is prone to false positives. PCR positivity may reflect colonization. Quantitative burden and host or imaging context help distinguish infection from colonization. Report sensitivity/specificity and, when possible, likelihood ratios and cutoff values.

Host evidence evaluation requires comprehensive consideration of immune status, clinical symptoms, laboratory indicators, and other dimensions. CD4+ T cell counts and lymphocyte subset analysis can reflect host immune functional status. Inflammatory markers including procalcitonin (PCT), C-reactive protein (CRP), and interleukin-6 (IL-6) assist in infection severity assessment and therapeutic monitoring.

Molecular diagnostic technology innovation

Metagenomic next-generation sequencing (mNGS) is an emerging, broad-range approach that can aid pathogen detection in lung cancer-associated OI. By sequencing nucleic acids directly from clinical samples-most commonly BALF-mNGS can reveal culture-negative or unculturable organisms and mixed infections, which is particularly useful in diagnostically challenging cases. In a multicenter retrospective study, Li et al. [69]. reported an OncomNGS workflow that jointly analyzes microbial reads and host copy-number variation from BALF, enabling single-test pathogen identification and detection of tumor-associated chromosomal abnormalities, and improving time-to-diagnosis in complex cases. These findings support feasibility on specific platforms; broader external validation is still needed.

Key advantages in this setting include a wide detection scope, the ability to detect multiple

organisms simultaneously, and turnaround that can be as short as 24-48 hours in streamlined laboratories. However, read counts provide only semi-quantitative information; interpretation should use normalized metrics (e.g., reads per million, genome coverage), thresholds relative to negative controls, and concordance with host/imaging context. In a cohort of 114 lung cancer patients with pulmonary infections, Hu Shan et al. [70]. reported an mNGS detection rate of 93.65% versus 12.70% for culture, with 61.02% mixed infections identified. Detection rate depends on specimen type, prior antibiotics, and the reference standard; positive results may reflect colonization or non-viable DNA and require clinicoradiologic correlation.

However, mNGS technology has certain limitations, inclusing relatively high costs with limited current adoption; result interpretation requires specialized knowledge with potential over-diagnosis or missed diagnosis; sensitivity for certain pathogens (such as mycobacteria) requiring improvement; inability to provide drug susceptibility information necessitating combination with traditional methods for treatment guidance. An analysis of 668 clinically suspected lung cancer or infection cases indicated BALF mNGS sensitivity of approximately 61.22% and specificity of 99.65%, but detection rates for concurrent M. TB infections remained lower than conventional molecular methods [71].

To maximize mNGS diagnostic value, synergistic application strategies with traditional methods are needed. For critically ill patients, simultaneous mNGS and traditional culture submission allows rapid pathogen diagnosis with the former and drug susceptibility guidance with the latter [72]. For chronic or complex infections, mNGS results can guide subsequent targeted culture. For suspected rare pathogen infections, mNGS has unique advantages.

Sample selection and processing are crucial for mNGS testing. BALF represents the preferred sample for pulmonary infection mNGS testing, with pathogen detection rates significantly higher than sputum and blood. Tissue samples, though more invasive, have higher diagnostic value for focal lesions [73]. Blood mNGS is primarily used for disseminated infection diagnosis, with lower sensitivity for localized pulmonary infections.

Differential diagnosis key points

Differential diagnosis of pulmonary lesions in lung cancer patients represents a major clinical challenge, requiring accurate distinction among OI, tumor progression, treatment-related lung injury, and other diseases.

ICI-related pneumonitis (CIP) represents a non-infectious lung injury receiving recent attention. The incidence of CIP is 3-5%, typically appearing within 2-3 months after treatment. A multicenter analysis conducted by Naidoo et al. [74] revealed overall CIP incidence of approximately 3-5% in cancer patients receiving PD-1/PD-L1 monotherapy, increasing to approximately 10% with combined CTLA-4 treatment. Key differences between CIP and infectious pneumonia include insidious onset with atypical/absent fever, mildly elevated inflammatory markers, normal/slightly elevated white blood cell counts, bilateral symmetric imaging lesions, negative pathogen detection, and favorable corticosteroid treatment response.

Targeted therapy-related ILD represents another important differential consideration. EGFR-TKI-related ILD incidence ranges from 3.9-5.3%, with osimertinib-related ILD of relatively higher incidence. Diagnosis requires combination of onset timing (usually weeks to months) while excluding infectious and tumor factors, with drug discontinuation and immunosuppressive treatment reversing most cases [75, 76]. Differentiation points include predominantly interstitial changes on imaging with frequent subpleural distribution, symptoms primarily of dry cough and dyspnea, and symptom improvement after targeted therapy discontinuation.

Radiation pneumonitis represents a common complication in patients receiving chest radiotherapy. Acute radiation pneumonitis typically occurs within 1-6 months after radiotherapy, primarily manifesting as inflammatory reactions within radiation fields. Chronic radiation pneumonitis is characterized primarily by fibrosis [77]. Differentiation points include lesion extent matching radiation fields, clear temporal relationships, symptom severity correlating with radiation dose, and favorable response to corticosteroids.

Differentiation between tumor progression and infection becomes particularly difficult when imaging appearances are similar. Key features of tumor progression covered elevated specific tumor markers, progressive imaging findings, tumor-related systemic symptoms, no response to anti-infective therapy, and final confirmation by pathology [74, 78].

To enhance the accuracy of differential diagnosis, multidisciplinary team (MDT) collaboration is recommended, integrating expertise from oncology, infectious diseases, pulmonary medicine, radiology, and pathology. In cases with challenging differential diagnosis, diagnostic therapy may be considered; close monitoring of patient responses is necessary, with timely adjustments to therapeutic strategies. Bronchoscopy combined with pathological and microbiological examinations serves as a key method for definitive diagnosis, but requires balancing benefits and risks.

Prevention and treatment strategies

Fungal infection management strategies

The principles of prevention and treatment for lung cancer-associated OI should be based on patients' immune status, pathogen types, and risk stratification, adopting a closed-loop strategy of "high-risk population prophylaxis-individualized anti-infective regimens-management of drug-drug interactions, enhanced supportive care and follow-up".

Primary prophylaxis for PJP has been proven to significantly reduce the incidence of PJP in high-risk patients. Takeuchi et al. [38] recommend including patients receiving ≥20 mg prednisone equivalent corticosteroids for ≥4 weeks, patients with persistent lymphopenia after chemotherapy/radiotherapy, or those undergoing immunotherapy with concurrent immunosuppression in trimethoprim-sulfamethoxazole (TMP-SMX) primary prophylaxis protocols. Alternative regimens include atovaquone, dapsone, and inhaled pentamidine. McAleese et al. [49] reported lung cancer patients undergoing radical radiotherapy that those receiving high-dose corticosteroids and chest irradiation had a significantly increased risk of PJP-related mortality; the implementation of TMP-SMX prophylaxis reduced the 2-year PJP-related mortality rate from 4% to 1%. Fan et al. [11] indicates that lung cancer patients developing PJP in ICI treatment have a significantly higher 28-day mortality compared to those in the non-ICI group. A systematic review by Heung et al. [13] highlighted the role of immune function in treatment selection: early broad-spectrum antifungal therapy can improve survival in neutropenic patients, whereas patients with partially preserved immune function can have their medications optimized based on pathogen detection results.

IPA management

IPA treatment utilizes triazole antifungals (voriconazole, isavuconazole, posaconazole) as treatment cornerstones, with echinocandin-class drugs suitable for azole-intolerant patients or severe combination therapy [79]. Lancet Respir Med review [17] indicates that IPA mortality in severe respiratory viral infection contexts (such as COVID-19, influenza) can reach 50%, supporting early antifungal therapy strategies in such high-risk patients.

Chen et al. [80] confirm that mNGS can simultaneously detect PJP and IPA within 24 hours, facilitating clarification of multi-pathogen infection components and treatment guidance. Marmor et al. [81] demonstrates that combining fungal serology (such as galactomannan), radiomics, and tumor markers in multimodal biomarker approaches can improve diagnostic accuracy for atypical fungal infections. Iadarola et al. [82] suggest respiratory proteomics analysis may provide potential biomarkers for early mixed pathogen identification, helping improve risk stratification for high-risk infections in lung cancer patients.

Voriconazole represents a first-line treatment for IPA, with loading doses of 6 mg/kg intravenous every 12 hours for two doses, followed by a maintenance doses of 4 mg/kg intravenous or 200 mg oral every 12 hours. Lamoth et al. [83] supported that voriconazole significantly reduces 28-day mortality in IPA patients in randomized controlled trials. Voriconazole demonstrates excellent lung tissue penetration and broad-spectrum anti-Aspergillus activity, but significant drug interactions and individualized pharmacokinetic differences require to be noticed.

Isavuconazole is a new-generation triazole drug with loading doses of 200 mg intravenous every 8 hours for 6 doses, followed by 200 mg daily maintenance. Literature indicates that isavuconazole tolerability is superior to voriconazole with fewer interactions with common anti-neoplastic drugs [84].

Dose of posaconazole extended-release tablets is 300 mg every 12 hours for 3 doses, followed by 300 mg daily. Beyond therapeutic effects, posaconazole prophylactic application in patients with hematologic malignancy significantly reduces IPA incidence.

Combination therapy may benefit refractory or severe IPA cases. Voriconazole plus caspofungin or voriconazole plus micafungin regimens demonstrate synergistic effects in multiple retrospective cohorts, improving fungal clearance rates and short-term survival [16, 83]. However, combination therapy simultaneously increases drug toxicity and interaction risks. It is recommended to use under MDT guidance.

Mycobacterial infection management strategies

TB treatment requires balancing anti-TB efficacy with anti-neoplastic treatment continuity. Standard TB treatment regimens involve four-drug intensive phase including isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months, followed by isoniazid and rifampin maintenance phase for 4 months. Lee et al. [85] reported that lung cancer patients with newly diagnosed active pulmonary TB using standard first-line anti-TB regimens significantly improved treatment completion rates, while advanced-stage tumors significantly increased treatment interruption risk. Fang et al. [86] indicated that active TB reactivation risk under ICI backgrounds can increase multiplicatively, with some populations reaching 35-fold higher risk than general populations.

Drug-resistant tuberculosis (MDR-TB) management proves more complex, requiring combination second-line drugs including fluoroquinolones, injectable agents, cycloserine, and para-aminosalicylic acid. New drugs like bedaquiline and delamanid demonstrate efficacy in MDR-TB treatment, but usage data in lung cancer patients remains limited, requiring careful benefit-risk assessment [87].

Coordination of TB treatment timing with anti-neoplastic therapy represents a key challenge. Generally, TB control for 2-8 weeks before initiating anti-neoplastic treatment is recommended, but concurrent treatment may be necessary due to rapid tumor progression [88]. Rifampin, as a potent CYP3A4 inducer, significantly reduces exposure to multiple anti-neoplastic drugs. Rifampin can reduce dasatinib area under the curve (AUC) by approximately 80-90%, imatinib AUC by 74%, with similar induction effects on crizotinib, osimertinib, and other tyrosine kinase inhibitors (TKIs) [89]. Combination with imatinib requires dose increase consideration, while combination with crizotinib needs strict efficacy monitoring.

NTM infection treatment proves more complex. American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) standard regimens for MAC include macrolides (azithromycin 500 mg daily or clarithromycin 1000 mg daily), rifabutin 300 mg daily, ethambutol 15 mg/kg daily, with treatment duration of at least 12 months. Li et al. [90] reported that lung MAC incidence within 10 years after lung resection in lung cancer patients was approximately 2.8%, with adjuvant chemotherapy or radiotherapy representing significant risk factors. For cavitary or severe infections, amikacin or streptomycin may be added for 2-3 consecutive months.

MABC infection treatment requires multi-drug combination regimens including amikacin, cefoxitin, and clarithromycin, with treatment duration of 12-18 months. M. kansasii demonstrates sensitivity to isoniazid, rifampin, and ethambutol, allowing TB-like regimens but requiring extended treatment duration of 18-24 months. ICI-related cases suggest increased rapidly growing mycobacterial (RGM) proportions. Li et al. [90] found that RGM comprised 73.3% of lung cancer NTM infections in ICI groups (with MABC accounting for 40%), with median onset time significantly earlier than non-ICI groups (12 vs. 21.5 months, P=0.004). NTM co-infections with PJP and IPA under immunosuppressive backgrounds are common, and consideration of simultaneous coverage strategies are required [14].

Comprehensive preventive measures

Vaccination represents an important measure for infection prevention in lung cancer patients.

Influenza vaccines should be administered before annual flu seasons, with inactivated vaccines recommended. Inactivated influenza vaccine administration in chemotherapy and immunosuppressed populations significantly reduces seasonal influenza incidence and hospitalization rates, with immune response rates in lung cancer patients approaching general cancer populations [91]. Vaccination timing should be arranged during chemotherapy cycle intervals, avoiding severe neutropenic periods.

Pneumococcal vaccines demonstrate important value in preventing Streptococcus pneumoniae infections. Patients ≥65 years or with immune dysfunction should receive 23-valent pneumococcal polysaccharide vaccine (PPSV23), with sequential 13-valent pneumococcal conjugate vaccine (PCV13) administration when necessary. Garcia Garrido et al. [92] showed the incidence of invasive pneumococcal disease in lung cancer patients was 393/100,000, which was significantly higher than that in general adults. While Mohr A et al. [93] reported that sequential PPSV23 + PCV13 vaccination in high-risk cancer patients can cover approximately 74% of high-risk serotypes with protection lasting approximately 5 years. Song YM et al. [94] showed pneumococcal vaccination rates of 73.4% in lung cancer survivors ≥65 years, but only 34.6% in non-lung cancer survivors <65 years, significantly below recommended levels, suggesting enhanced vaccine promotion in younger cancer patients was needed.

Recombinant zoster vaccine (RZV) is recommended for adults aged ≥50 years and for immunocompromised adults aged ≥19 years. It is a non-live, two-dose series (0 and 2-6 months; may be accelerated to 1-2 months in those who will undergo significant immunosuppression) and is preferred over live attenuated zoster vaccines, which are not recommended; when feasible, complete vaccination before intensive immunosuppression, though RZV can be given during chemotherapy, ICIs, or targeted therapy with expected transient reactogenicity [93].

Antimicrobial stewardship (AMS) should emphasize obtaining cultures before therapy, early narrowing based on microbiology and clinical response, and using the shortest effective, syndrome-specific durations rather than a fixed 7-10 days. In FN, for hemodynamically stable patients with negative cultures, de-escalation and discontinuation can be considered after ≥48 hours afebrile with an improving absolute neutrophil count (ANC) trajectory. Unnecessary broad-spectrum combinations and duplicative coverage should be avoided. Prompt adjustment should be made to susceptibility results, and results should be enhanced while multidrug-resistant organism prevention measures are being implemented. Antibacterial prophylaxis with an oral fluoroquinolone is reserved for patients with anticipated profound and prolonged neutropenia (e.g., ANC <100/μL for >7 days) or high overall FN risk; most solid-tumor regimens do not meet these criteria [95]. OI prevention should prioritize PJP prophylaxis in patients on prolonged systemic corticosteroids (≥20 mg prednisone-equivalent for ≥4 weeks), with prior PJP, or with marked lymphopenia; TMP-SMX is first-line, with atovaquone or dapsone (after G6PD testing) or inhaled pentamidine as alternatives; primary mold-active antifungal prophylaxis is rarely indicated in solid tumors and requires careful assessment of drug interactions and hepatotoxicity [83]. Prolonged or high-dose antimicrobial exposure, particularly when combined with corticosteroids, may disrupt the microbiome and dampen anti-tumor immune responses during immunotherapy, underscoring judicious use [55]. A systematic review by Tong et al. found that empirical antifungal therapy in lung cancer patients receiving chemotherapy with pulmonary infections reduced short-term infection-related mortality, but resistance and recurrence warrant close follow-up and deprescribing when supported by clinical and microbiologic data [56]. Environmental measures should include strict hand hygiene and routine cleaning/disinfection; single rooms for high-risk patients with high-efficiency particulate air (HEPA) filtration and positive-pressure strategies during hospital construction or high-exposure periods; avoidance of flowers and potted plants; visitor masking with limits on duration and numbers; and food safety (no raw/undercooked meats or eggs and no unpasteurized dairy, while avoiding overly restrictive “neutropenic diets”); inadequate air filtration or construction-related exposure can increase airborne Aspergillus spores and invasive disease risk, which is particularly relevant for long-stay immunosuppressed lung cancer patients [61].

It has been proven that nutritional support is crucial for maintaining immune function. Malnourished patients should receive nutritional assessment and intervention with enteral or parenteral nutrition support when necessary. Micronutrient supplementation like vitamin D, zinc, and selenium, other help improve immune responses [11]. Strict glycemic control avoiding hyperglycemia-induced immunosuppression, smoking cessation, alcohol limitation, and lifestyle improvements reduce infection and cardiopulmonary complication risks.

Clinical practice pathways and recommendations

Risk-stratified clinical pathways

Establishing standardized risk stratification systems provides the foundation for optimizing lung cancer-associated OI management. Risk assessment requires comprehensive consideration of host, treatment, and environmental factors. Patients are categorized into low-, moderate-, and high-risk levels. Specifically, low-risk patients are defined as those aged <65 years, without significant comorbidities, receiving standard chemotherapy or targeted therapy, and experiencing mild and short-duration immunosuppression. Moderate-risk patients refer to those aged ≥65 years or with comorbidities such as diabetes, or COPD, receiving platinum doublet chemotherapy or concurrent chemoradiotherapy, and expected to have moderate immunosuppression. High-risk patients are those with multiple risk factors, receiving high-intensity chemotherapy or high-dose corticosteroid treatment, and anticipated to develop severe and persistent immunosuppression.

It is reported that in advanced NSCLC patients receiving immunotherapy, poor baseline Eastern Cooperative Oncology Group performance status and concurrent infections are significant mortality risk factors, while MDT intervention can reduce infection-related death risk by approximately 50% [96]. Outpatient management strategies should be targeted at low-to-moderate risk patients, with specialized tumor-infection outpatient clinics recommended and risk-stratified follow-up frequencies implemented (low-risk patients followed up every 4-6 weeks, moderate-risk patients every 2-4 weeks, anf high-risk patients every 1-2 weeks). Additionally, follow-up content includes symptom inquiry, physical examination, complete blood count and inflammatory marker testing, chest CT when necessary, plus vaccination and health education.

Standardized early warning systems should be established, with timely inpatient referral when patients develop persistent fever >38.5°C over 24 hours, dyspnea or SpO_2 <95%, severe neutropenia with infection signs, new pulmonary lesions on imaging, or multi-organ dysfunction.

Inpatient management strategies and multidisciplinary collaboration models

Inpatient care should prioritize early, structured assessment and timely multidisciplinary input. Within 24 hours of admission, a standardized evaluation should be completed, and an individualized plan should be initiated with a 48-72 hour antimicrobial review scheduled for de-escalation or escalation. MDT discussions should be triggered for patients who are critically ill, have diagnostic uncertainty after initial workup, present discordant imaging-microbiology-host findings, or are candidates for invasive diagnostics (bronchoscopy, biopsy). The core MDT should include thoracic oncology, pulmonology, infectious diseases, radiology, microbiology, pharmacy, and nursing, with clear roles, documentation standards, and a single point-of-contact. Regular weekly tumor-board style meetings with defined membership and processes have been associated with improved diagnostic throughput, time-to-treatment, and fewer duplications, while 24/7 rapid consultation capacity supports urgent infectious issues [97]. Clinical pharmacists optimize therapy selection and dosing (renal/hepatic adjustment), manage drug-drug interactions, provide therapeutic drug monitoring where indicated, monitor QTc and hepatotoxicity, and lead stewardship audits; pharmacist-nursing collaboration strengthens AMS implementation and can reduce multidrug-resistant organism events [98].

Patient education and follow-up management

Bidirectional impact of infection and anti-infective therapy on the antitumor efficacy of ICIs

Multiple clinical and translational studies indicate that infectious states and related medica-

tions can significantly modulate the antitumor efficacy of ICIs [35]. In real-world NSCLC cohorts, active bacterial pulmonary infection around ICI initiation is associated with worse survival outcomes and higher early discontinuation rates [35]. Systemic antibiotic exposure during the peri-ICI window (approximately -60 to +60 days) has been repeatedly linked to diminished ICI efficacy across tumor types, plausibly via loss of gut microbiome diversity and depletion of key commensals such as Akkermansia [100]. Similarly, concomitant proton pump inhibitor use, another modifier of the microbiome, has been independently associated with poorer survival on ICIs [101]. Interventional evidence shows that restoring the microbiota with fecal microbiota transplantation (FMT) can reinstate responses in some PD-1-refractory melanoma patients, supporting a causal "microbiome → antitumor immunity" pathway [102]. In addition, baseline systemic corticosteroid use (e.g., ≥10 mg prednisone equivalent at ICI initiation) correlates with substantially impaired ICI efficacy, suggesting that high-dose or prolonged steroids given for infections or other indications can suppress antitumor immunity and carry clinical costs [103]. In regions with high or intermediate TB prevalence, ICI-associated TB reactivation risk is increased, often prompting interruption of immunotherapy and introducing rifampin-related drug-drug interaction challenges with multiple anticancer agents, further affecting tumor control [40].

Molecular mechanisms underlying microbiome-ICI interactions

Recent mechanistic studies have elucidated how specific microbial metabolites directly modulate ICI efficacy through T cell reprogramming [63, 104]. Short-chain fatty acids, particularly butyrate and pentanoate produced by commensal bacteria such as Faecalibacterium prausnitzii, Roseburia intestinalis, and Clostridium species, enhance CD8+ T cell function through dual mechanisms: histone deacetylase inhibition - mediated epigenetic reprogramming and metabolic rewiring via the mTOR pathway [105, 106]. Butyrate treatment increases acetylation of STAT1 and histones in CD8+ T cells, upregulating expression of CD25, IFN-γ, and TNF-α, thereby amplifying cytotoxic activity against tumor cells [105]. Mechanistically, butyrate uncouples the tricarboxylic acid cycle from glycolytic input, promoting oxidative phosphorylation through sustained glutamine utilization and fatty acid catabolism, which enhances CD8+ T cell memory potential and longevity [106, 107]. In gastric cancer models, butyrate signals through G protein-coupled receptor 109A to upregulate homeobox protein HOPX in CD8+ T cells, directly enhancing their tumor-killing capacity [108]. Trans-kingdom microbiota analysis has identified that not only bacteria but also eukaryotic microbes (Naumovozyma serpens, Hanseniaspora pseudoburtonii) contribute to ICI responsiveness through metabolite production [109]. Indole derivatives such as indole-3-propionic acid and indole-3-aldehyde (I3A) activate γδ T cells and Tc1 effector functions via aryl hydrocarbon receptor (AhR)/CREB signaling while simultaneously suppressing the immunosuppressive IDO1/kynurenine/AhR axis, thereby attenuating regulatory T cell (Treg)-mediated immunosuppression [104]. Conversely, certain metabolites such as kynurenine (a tryptophan metabolite) and secondary bile acids drive ICI resistance by polarizing macrophages toward an M2 immunosuppressive phenotype and inducing CD8+ T cell exhaustion through PD-L1 upregulation and myeloid-derived suppressor cell (MDSC) expansion [104].

Differential impact of antimicrobial classes on ICI efficacy

The temporal window and antimicrobial class significantly determine ICI outcomes in NSCLC [110, 111]. In a 2024 ASCO cohort analysis of older adults with advanced NSCLC, antibiotic exposure within 60 days before ICI initiation was associated with increased 3-year mortality for ICI monotherapy (HR 1.24, 95% CI 1.05-1.46), with fluoroquinolones showing the strongest negative association (HR 1.41, 95% CI 1.1-1.8) [112]. Mechanistic studies reveal class-specific effects, e.g. β-lactam antibiotics (particularly cephalosporins and penicillins) significantly shorten OS and progression-free survival (PFS) in ICI-treated patients, whereas quinolones show variable effects depending on spectrum and duration [113]. Importantly, antibiotic-associated harm extends to chemoimmunotherapy combinations, contradicting earlier assumptions that chemotherapy might buffer microbiome disruption; in a 2,028-patient cohort, antibiotic exposure in both the -60-day

and -60/+42-day windows correlated with reduced objective response rate (ORR) and shorter PFS in platinum-doublet plus anti-PD-(L)1 regimens [110]. Differential antibacterial spectra explain divergent outcomes: broad-spectrum β-lactams deplete butyrate-producing Faecalibacterium and Roseburia species, while narrow-spectrum agents cause less collateral microbiome damage [113]. proton pump inhibitors (PPIs) further compound microbiome disruption and independently predict worse ICI outcomes (adjusted HR for OS approximately 1.3-1.5), likely via pH-mediated alterations in microbial diversity and short-chain fatty acids (SCFAs) production [114]. A 2025 systematic review of NSCLC patients confirmed that PPI and antibiotic co-exposure within 1 month before ICI initiation correlates with diminished efficacy, whereas probiotic supplementation and plant-based diets align with improved outcomes [115].

TB treatment and drug-drug interactions

TB reactivation risk is elevated 6- to 9-fold in ICI-treated lung cancer patients compared with TKI-treated controls, necessitating baseline screening in intermediate- to high-burden regions [40]. Once diagnosed, TB treatment introduces complex drug-drug interactions: rifampin, a potent CYP3A4 inducer, reduces exposure to multiple TKIs by 70%-90% (dasatinib AUC reduced approximately 85%, imatinib AUC reduced approximately 74%, osimertinib exposure substantially decreased) [89]. Rifampin co-administration with crizotinib or osimertinib requires strict therapeutic drug monitoring (TDM) and may necessitate empiric TKI dose escalation or substitution with rifabutin (a weaker CYP3A4 inducer), though rifabutin data in oncology populations remain limited [89]. Conversely, ICIs themselves do not undergo significant cytochrome P450 metabolism, allowing concurrent ICI and TB therapy without direct pharmacokinetic interference; however, prolonged corticosteroid use for TB-associated immune reconstitution inflammatory syndrome can blunt ICI efficacy [103].

Targeted clinical strategies to preserve ICI efficacy during infection management

Antimicrobial stewardship programs should prioritize narrow-spectrum, culture-directed therapy, early de-escalation (within 48-72 hours of pathogen identification), and syndrome-specific short-course regimens rather than reflexive 7- to 10-day courses, particularly in the peri-ICI window (-60 to +42 days relative to ICI initiation) [111, 116]. When empiric broad-spectrum therapy is unavoidable, clinicians should preferentially select agents that spare anaerobic butyrate producers, though carbapenem overuse risks resistance [113]. Fluoroquinolone prophylaxis, while effective for FN prevention in profound neutropenia (ANC <100/μL for >7 days), should be avoided in solid tumor patients receiving ICIs unless absolute indications exist, given documented survival detriment [95, 112]. FMT from ICI responders can restore therapeutic sensitivity in refractory patients: in a landmark melanoma trial, 30% of anti-PD-1-refractory patients achieved objective responses after FMT from responders, with engraftment of donor Akkermansia, Faecalibacterium, and Ruminococcus correlating with clinical benefit [102]. Probiotic supplementation with Faecalibacterium prausnitzii strain EXL01 or multi-strain consortia (Bifidobacterium, Lactobacillus) enhances ICI efficacy in preclinical models and early-phase clinical trials, though strain-specific effects and optimal timing (concurrent vs. sequential with ICI) require validation [109, 117]. Dietary fiber intake (≥20 g/day) supports endogenous SCFAs production and correlates with improved PFS in ICI-treated melanoma and NSCLC cohorts [115]. High-dose systemic corticosteroids (≥10 mg prednisone-equivalent daily at ICI initiation) independently predict poor ICI outcomes (median OS reduction of approximately 6-8 months in multiple tumor types), necessitating judicious steroid use and rapid tapering for infection-related indications [103]. For patients requiring prolonged immunosuppression for severe infections, temporary ICI interruption is reasonable during active, uncontrolled infection with concurrent high-dose corticosteroids (≥20 mg/day for >2 weeks); ICI should be resumed after infection control and steroid taper to <10 mg/day. ICI dose reduction is not recommended, as standard fixed dosing (e.g., pembrolizumab 200 mg Q3W, nivolumab 240 mg Q2W) already accounts for population pharmacokinetic variability; instead, extending dosing intervals (e.g., Q4W instead of Q3W) during infection may be considered if necessary [118]. PJP prophylaxis (TMP-SMX) should be initiated before starting ICIs in high-risk patients (ALC <500/μL, prior

PJP, anticipated prolonged corticosteroids) rather than reactively, and continued throughout ICI therapy plus 4-6 weeks post-discontinuation or until immune recovery [38]. In TB-endemic regions, latent TB screening (interferon-γ release assay) before ICI initiation is recommended, with preventive therapy (rifampin 4 months or isoniazid 9 months) completed before or concurrent with ICI when feasible [40]. For patients developing active TB on TKIs, coordination with infectious disease specialists to substitute rifampin with rifabutin (reducing CYP3A4 induction approximately 70%) or use rifampin-sparing regimens (e.g., moxifloxacin-based) is recommended if rifamycin-TKI co-administration is unavoidable [89]. ICI-treated patients with TB can usually continue rifampin-based regimens without dose adjustment, though vigilance for paradoxical worsening (immune reconstitution) is warranted. Serial monitoring should include monthly ALC and CD4 counts, prompt infection workup for fever or symptoms, and consideration of FMT or probiotic rescue if broad-spectrum antibiotics were unavoidable and ICI response plateaus. Tracking antibiotic days of therapy (DOT) per 1,000 ICI treatment days as a stewardship metric is recommended [116]. Taken together, clinical trade-offs should prioritize rapid, precise infection control to avoid ICI delays, antimicrobial stewardship to prevent or minimize broad-spectrum antibiotics and unnecessary PPI exposure, use of the lowest effective steroid dose for the shortest duration when systemic steroids are required, implementation of baseline TB screening and risk-adapted management in endemic settings, and consideration of probiotic strategies or clinical trial pathways to maximize ICI benefit while controlling infection (**Table 5**).

Future perspectives

Risk prediction models and artificial intelligence applications

Big-data pipelines and machine learning can enable individualized, time-updating risk prediction for OI by integrating clinical variables, imaging, laboratory data, and multi-omics. Deep learning combined with radiomics may auto-detect CT patterns suggestive of infection and support differential diagnosis, while clinical decision support systems that encode guidelines and local antibiograms can assist non-infectious-disease oncologists with empiric choice, dosing, monitoring, and de-escalation. To be clinically reliable, models should undergo external validation, calibration assessment, and impact analysis; include transparency on inputs and thresholds; be monitored for dataset shift and fairness; and be embedded into workflows with audit trails and stewardship oversight.

Microbiome research

Lung cancer patients frequently exhibit gut and airway dysbiosis, which may increase OI susceptibility and modify responses to immunotherapy. ICIs, antibiotics, corticosteroids, and PPIs can perturb the microbiome; antibiotic exposure, in particular, is linked to Clostridioides difficile infection and may blunt ICI efficacy. Microbiome-derived biomarkers (e.g., taxa signatures or metabolites) are promising for risk stratification and early infection prediction, but require standardized methods and prospective validation. Probiotics and FMT are potential interventions; in oncology populations, safety and interaction with anti-cancer therapy must be carefully evaluated, and current use should be confined to guideline-supported indications or clinical trials.

Precision medicine and immune monitoring

Precision tools can individualize diagnostics, prophylaxis, and dosing in lung cancer-associated OI. For triazoles, CYP2C19 genotype strongly influences voriconazole exposure; pairing preemptive genotyping with early TDM improves target attainment and safety. Practical trough targets are approximately 1-5.5 mg/L for voriconazole and ≥1.0 mg/L for posaconazole; routine TDM is generally unnecessary for isavuconazole, which shortens the QT interval and may be preferred in patients with baseline QT prolongation [83, 99]. Host factors remain central to risk stratification. Persistent lymphopenia and prolonged/high-dose corticosteroids signal PJP risk and can trigger or extend prophylaxis [38]. In moderate- to high-TB-burden settings, baseline IGRA and region-adapted management are reasonable when planning ICI-based therapy, given cohort signals for TB reactivation [41]. Immune monitoring should be pragmatic and repeatable.

Table 5. Grading system for anti-infective therapy impact on ICI efficacy

Grade	Impact Level	Mechanism of ICI Interference	Clinical Examples	Mitigation Strategies	ICI Management Recommendation
Grade 0	Beneficial/ Neutral	Infection prevention without microbiome disruption; vaccine-induced immune activation may enhance anti-tumor immunity	• Vaccinations (influenza, pneumococcal, zoster, COVID-19) • Targeted prophylaxis (TMP-SMX ≤3 days/ week) • Narrow-spectrum antibiotics <3 days duration	• Prioritize vaccination before ICI initiation • Use narrowest spectrum for shortest duration	Continue ICI as planned; encourage vaccinations
Grade 1	Minimal	Short-duration therapy or agents with negligible microbiome impact; no significant DDI	• TMP-SMX treatment ≤21 days • Atovaquone • Echinocandins (caspofungin, micafungin) • Dapsone • Pentamidine (inhaled) • Targeted antivirals (acyclovir ≤14 days)	• No special intervention required • Complete full treatment course • Routine ICI efficacy monitoring	Continue ICI; no dose adjustment or delay needed
Grade 2	Moderate	Prolonged therapy (>3 weeks) causing moderate microbiome shifts; mild DDI requiring monitoring; or moderate hepatotoxicity risk delaying chemotherapy cycles	• Voriconazole >4 weeks • Fluoroquinolones 10-14 days • Macrolides (azithromycin/clarithromycin) >3 weeks • Posaconazole (prolonged) • Rifabutin-based TB/NTM regimens • Isavuconazole (long-term)	• Microbiome support: Consider probiotics (Lactobacillus, Bifidobacterium) if antibiotics >7 days (limited evidence in oncology; not FDA-approved for this indication) • Avoid concurrent PPI if possible • Complete necessary course but avoid unnecessary prolongation • Monitor tumor response at 8-12 weeks	Continue ICI with enhanced monitoring; assess tumor response q8-12 weeks; if progression, consider infection vs. tumor vs. pseudoprogression
Grade 3	High	Severe microbiome disruption (broad-spectrum antibiotics during peri-ICI window) OR cancer therapy interruption due to DDI (rifampin-TKI) OR prolonged high-dose corticosteroids impairing T-cell function	• Broad-spectrum antibiotics during ICI window (-60 to +60 days from ICI start): carbapenems, pip-tazo, 3rd-gen cephalosporins >7 days • Rifampin-based TB regimen causing TKI/ chemo interruption • Corticosteroids ≥10 mg prednisone × >4 weeks for infection (e.g., severe PJP) • Multiple concurrent broad-spectrum agents	• Use narrowest effective spectrum • Steroid-sparing: taper ASAP; consider steroid alternatives if feasible • Rifampin alternatives: use rifabutin or non-rifamycin regimen • FMT consideration: if recurrent *C. difficile* during ICI • Probiotic supplementation: case-by-case (emerging data) • Avoid concurrent PPI	ICI continuation decision: Case-by-case MDT discussion. Options: • Hold ICI temporarily (2-4 weeks) if severe infection requiring high-dose steroids • Continue ICI if infection controlled and steroids tapered • Monitor closely for progression; if PD, consider re-biopsy to exclude pseudoprogression
Grade 4	Severe	ICI discontinuation or prolonged interruption (>6 weeks); life-threatening infection; or grade ≥3 irAE requiring long-term immunosuppression (>2 months high-dose steroids)	• Life-threatening sepsis, ARDS requiring ICI cessation • Grade 4 irAE (e.g., pneumonitis, colitis) requiring prednisone ≥1 mg/kg × >6 weeks • Disseminated fungal infection requiring prolonged multi-agent antifungals • MDR-TB or disseminated TB requiring ICI hold	• Focus on infection cure first • Defer ICI until infection controlled and immune recovery • Consider alternative cancer therapy (chemotherapy, targeted therapy, clinical trial) • ICI rechallenge: MDT discussion after infection resolution (typically ≥4-8 weeks); consider toxicity risk vs. tumor control benefit	Hold ICI; prioritize infection treatment and supportive care. Rechallenge decision factors: • Infection cure documented • Immune recovery (ALC >500, CD4 >200) • Off high-dose steroids • Patient performance status improved • Tumor progression necessitating ICI despite risk • Rechallenge protocol: restart at same dose with close monitoring; consider prophylaxis

Comprehensive assessment of patients' immune status can be achieved by tracking ALC and CD4+ T cells to inform PJP prophylaxis initiation and de-escalation. Additionally, reassessment should be performed when there are changes in treatment intensity or steroid exposure changes [38]. When invasive sampling is unsafe or inconclusive, sequencing-based methods can complement standard tests; mNGS can integrate host and microbial signals in complex cases, while parallel conventional methods remain necessary for susceptibility testing and to avoid over-calling colonization [13, 69].

Future research directions

Priorities include multicenter prospective studies that account for patient heterogeneity; external validation and calibration of artificial intelligence/risk models with real-world impact evaluation; standardized, transferable risk scores; mechanistic work to clarify the microbiome-immunotherapy-infection causal chain; randomized or adaptive trials testing individualized prophylaxis and TDM/genotype-guided strategies; and international data-sharing frameworks with harmonized phenotypes and reproducible analytics to enhance quality and generalizability.

Conclusion

Lung cancer-associated OI in the immunotherapy and multimodal anti-neoplastic strategy era demonstrate characteristics of broad pathogen spectra, complex pathogenic mechanisms, and substantial diagnostic and therapeutic challenges. Ranging from fungi (PJP, IPA) to mycobacteria (TB, NTM), to viruses and bacteria, multiple pathogen types coexist against the backdrop of immune dysfunction, lung structural damage, and healthcare-associated exposures, significantly affecting patient survival and the continuity of antineoplastic treatment. Effective management relies on a three-dimensional "imaging-pathogen-host" evidence chain and multimodal diagnostics, integrating prophylaxis for high-risk populations, individualized anti-infective therapy, standardized vaccination, and antimicrobial stewardship to construct comprehensive, risk-stratified closed-loop prevention and treatment systems. In the future, prospective multicenter studies should be conducted to elucidate the causal chain of "microbiome-immunotherapy-infection outcomes" and establish standardized risk scoring systems. Additionally, the application of artificial intelligence and multi-omics technologies in clinical decision support should be promoted to realize precise diagnosis, targeted treatment, and long-term survival benefits for patients with lung cancer-associated OI.

Disclosure of conflict of interest

None.

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