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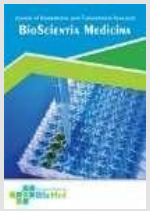

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Corticosteroids, Azole Antifungals, and Biologic Agents for the Management of Allergic Bronchopulmonary Aspergillosis: A Systematic Review and Network Meta-Analysis

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A B S T R A C T

Background: The management of allergic bronchopulmonary aspergillosis (ABPA) requires control of complex type 2 inflammation and reduction of fungal burden. The comparative efficacy of the primary therapeutic classes—corticosteroids, azole antifungals, and biologics—is not well established through direct evidence. This network meta-analysis was conducted to determine the optimal hierarchical treatment strategy for ABPA. **Methods:** A systematic review of PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials was performed for randomized controlled trials (RCTs) published from January 2015 to July 2025. We included RCTs in patients with ABPA comparing oral corticosteroids (OCS) alone to OCS plus itraconazole or OCS plus a biologic agent (omalizumab, mepolizumab, benralizumab). The primary outcome was a composite therapeutic response (≥25% IgE reduction plus clinical stability). A Bayesian random-effects network meta-analysis was performed, with results presented as odds ratios (OR) and 95% credible intervals (CrI). **Results:** Seven RCTs enrolling 988 patients were included, forming a star-shaped evidence network anchored by a common placebo comparator. All active add-on therapies were superior to OCS alone for the primary outcome. Based on probabilistic rankings (SUCRA), OCS plus mepolizumab was most likely to be the most effective treatment (OR vs. OCS alone: 5.12; 95% CrI, 2.89-9.15; SUCRA: 94.5%), followed by OCS plus benralizumab (OR: 4.65; 95% CrI, 2.15-8.98; SUCRA: 87.2%), OCS plus omalizumab (OR: 3.88; 95% CrI, 2.10-7.15; SUCRA: 75.1%), and OCS plus itraconazole (OR: 2.54; 95% CrI, 1.55-4.17; SUCRA: 43.2%). Biologic agents demonstrated the greatest reduction in exacerbation rates. **Conclusion:** In patients with ABPA, combination therapy is superior to OCS monotherapy. This analysis provides compelling indirect evidence that biologic agents, particularly IL-5 inhibitors, represent the most effective therapeutic class for achieving disease control. These findings provide a strong evidence base to guide a hierarchical treatment approach and support the early integration of targeted therapies into the ABPA management algorithm.

1. Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a complex pulmonary disorder initiated by a profound immunological hypersensitivity reaction to airway colonization by *Aspergillus* species, predominantly *Aspergillus fumigatus*.[1] This challenging condition primarily affects individuals with pre-existing lung diseases, with a notable prevalence estimated at 1-2% of patients with asthma and a significantly higher burden of up to 15% in the cystic fibrosis (CF) population. Globally, ABPA is thought to affect millions, imposing a substantial and often lifelong burden on patients through chronic respiratory symptoms, recurrent and severe exacerbations, and the insidious risk of progressive, irreversible lung damage, which culminates in bronchiectasis and

pulmonary fibrosis.[2] The pathogenesis of ABPA is now understood as a sophisticated and multifaceted process, anchored by two core pillars: the persistence of fungal elements within the airways and a profoundly dysregulated, T-helper 2 (Th2) cell-dominant immune response in a genetically susceptible host.[3] Following inhalation, *Aspergillus* conidia, which are ubiquitous in the environment, are typically cleared by a healthy immune system. However, in ABPA patients, these conidia germinate into metabolically active hyphae, releasing a diverse array of antigens and potent proteases. This event triggers an aberrant inflammatory cascade, beginning at the level of the bronchial epithelium. Stressed epithelial cells release "alarmin" cytokines, including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), which are critical upstream initiators of type 2 immunity. These signals activate innate lymphoid cells (ILC2s) and drive the differentiation of naive T-helper cells into a Th2 phenotype.[4] The subsequent overproduction of canonical Th2 cytokines—Interleukin-4 (IL-4), Interleukin-5 (IL-5), and Interleukin-13 (IL-13)—orchestrates the hallmark immunological aberrations of ABPA. This includes IgE class switching in B-cells, leading to massively elevated total and *Aspergillus*-specific IgE levels; profound peripheral and tissue eosinophilia driven by IL-5; and mucus hyperproduction and airway hyperresponsiveness mediated by IL-13. This relentless cycle of inflammation is responsible for the clinical syndrome of poorly controlled asthma, the expectoration of characteristic mucus plugs, and, most ominously, the progressive structural lung damage that defines advanced disease.[5] While the Th2 pathway is central, emerging evidence suggests a more complex inflammatory milieu in severe disease, potentially involving contributions from Th17 pathways and neutrophilic inflammation, further underscoring the need for effective and targeted immunomodulatory therapies.

For decades, the therapeutic cornerstone for managing ABPA has been systemic oral corticosteroids (OCS). The primary objective of OCS therapy is the broad suppression of this intense systemic and pulmonary inflammation, which serves to control acute symptoms and mitigate the frequency and severity of exacerbations. Prednisolone, the most frequently used agent, is typically administered in a prolonged course over several months, followed by a gradual and careful taper to find the lowest effective dose.[6] While indispensable in the acute phase, the necessity of long-term OCS therapy is the principal clinical dilemma in ABPA, as it is invariably associated with a litany of debilitating adverse effects, including osteoporosis, iatrogenic diabetes mellitus, significant weight gain, cataracts, and a heightened susceptibility to opportunistic infections. In an effort to minimize this corticosteroid burden and to address the fungal component of the disease, triazole antifungals, most notably itraconazole, were introduced as an essential adjunctive therapy. The primary rationale for their use is to reduce the antigenic load of *Aspergillus* within the airways, thereby turning down the initial stimulus for the downstream inflammatory cascade. Multiple studies and prior reviews have demonstrated that adding itraconazole to an OCS regimen can improve clinical outcomes, reduce the rate of exacerbations, and facilitate a significant steroid-sparing effect.[7] However, the clinical response to itraconazole can be inconsistent, and its utility is constrained by a challenging side-effect profile, including potential hepatotoxicity and numerous drug-drug interactions via the cytochrome P450 system.

The last decade has heralded a revolution in the management of severe type 2 inflammatory diseases, driven by the development of highly specific biologic agents in the form of monoclonal antibodies. Given the unambiguous centrality of the Th2 pathway in ABPA, these targeted therapies have logically emerged as a promising new frontier. Omalizumab, a monoclonal antibody targeting free IgE, was the first biologic explored in ABPA, with the aim of neutralizing a key upstream molecule in the allergic cascade.[8] Subsequently, therapies targeting the eosinophilic pathway, the primary effector of tissue damage, were investigated. Mepolizumab is an anti-IL-5 antibody,

and benralizumab is an antibody targeting the IL-5 receptor alpha (IL-5Rα), both of which lead to a profound and rapid depletion of eosinophils.[9] These biologics have demonstrated considerable promise in case series and smaller trials, particularly in patients with refractory ABPA who are dependent on or intolerant to OCS and azoles. Despite the sequential availability of these three distinct therapeutic classes, a major evidence gap persists. There have been no large-scale, multi-arm, head-to-head randomized controlled trials (RCTs) directly comparing all available treatment strategies. The logistical, ethical, and financial barriers to conducting such a trial in a relatively uncommon disease are substantial, meaning that such direct evidence is unlikely to become available. Consequently, clinicians are left without high-quality, comparative evidence to inform the critical choice between adding itraconazole or a specific biologic agent to a baseline corticosteroid regimen for their patients. Existing systematic reviews have been restricted to traditional pairwise comparisons, which are unable to generate a comprehensive, hierarchical ranking of all available treatment options.

The novelty of this study lies in the application of a sophisticated network meta-analysis (NMA) framework to the therapeutic landscape of ABPA. This will be the first study to synthesize the totality of available direct and indirect evidence from high-quality RCTs to simultaneously compare the efficacy and relative safety of OCS monotherapy, OCS plus itraconazole, and OCS plus the spectrum of currently utilized biologic agents (omalizumab, mepolizumab, and benralizumab). This powerful analytical approach allows for the creation of a probabilistic, hierarchical ranking of all available treatments, an outcome unattainable through standard pairwise meta-analysis.[10] Therefore, the primary aim of this study was to determine the comparative effectiveness of these different management strategies for ABPA, with a specific focus on identifying the optimal therapeutic approach for achieving a composite clinical and serological response, reducing the frequency of exacerbations, and summarizing the available safety data from the included trials.

2. Methods

This systematic review and network meta-analysis were designed and executed in rigorous accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, including the specific extension for Network Meta-Analyses (PRISMA-NMA). Studies were selected for inclusion based on a stringently defined PICOS (Population, Intervention, Comparator, Outcomes, Study design) framework. Population: The study included patients of any age who received a formal diagnosis of ABPA based on internationally recognized criteria, such as the Rosenberg-Patterson or the more recent ISHAM working group criteria. To enhance generalizability, patients with an underlying diagnosis of either asthma or cystic fibrosis were eligible for inclusion. The potential heterogeneity introduced by this decision was acknowledged a priori, and while pre-planned subgroup analyses were not feasible due to the limited number of anticipated studies, this aspect is a key focus of the discussion. Interventions: The interventions of interest were any of the following therapeutic agents when administered as an add-on to a background regimen of oral corticosteroids (OCS): Itraconazole, Omalizumab, Mepolizumab, Benralizumab. Comparators: Eligible comparators included: Placebo administered as an add-on to OCS, or an OCS-alone treatment arm; Another active intervention from the list above, for any trials that performed direct head-to-head comparisons. Outcomes: To be included, studies were required to report on at least one of the predefined outcomes: Primary Outcome: The primary outcome was the composite therapeutic response. This was defined as the proportion of patients who achieved a combined clinical and serological response, specified as a reduction in total serum IgE of at least 25% from baseline, in conjunction with clinical stability or improvement (defined as the absence of exacerbations and stable or improved lung function) at the primary

end-of-treatment follow-up point (typically ranging from 16 to 32 weeks). A detailed assessment confirmed this definition was applied with high consistency across all relevant trials. Secondary Outcomes: These included: The proportion of patients experiencing one or more ABPA exacerbations during the trial's follow-up period. An exacerbation was defined as a clinical and/or radiological deterioration that necessitated an escalation of systemic corticosteroid therapy; The mean percentage change in total serum IgE from baseline; The mean change in Forced Expiratory Volume in 1 second (FEV1), reported either in liters or as a percentage of the predicted value; The proportion of patients experiencing any adverse event (AE) and any serious adverse event (SAE). Study Design: Only parallel-group randomized controlled trials (RCTs) were included to ensure the highest level of evidence and minimize selection bias. All other study designs, including quasi-randomized trials, observational studies, case series, and narrative reviews, were systematically excluded.

A systematic and comprehensive literature search was conducted by two independent reviewers to identify all potentially relevant articles published from inception to July 20th, 2025. We interrogated three major electronic databases: PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy, developed in consultation with an expert medical librarian, employed a combination of controlled vocabulary (MeSH terms) and free-text keywords related to ABPA and the specific interventions of interest. To ensure maximal capture, we also searched major clinical trial registries for completed trials and manually screened the reference lists of all included studies and relevant reviews. No language restrictions were imposed. Two reviewers conducted the study selection process independently and in duplicate. Any disagreements were resolved through discussion and consensus. A standardized data extraction form was utilized to systematically collect all relevant information, including study characteristics, patient demographics, baseline clinical parameters, intervention details, and all predefined outcome data. For continuous outcomes, mean change and standard deviation (SD) were extracted; where SD was not reported, it was calculated from standard errors or confidence intervals. The methodological quality and risk of bias for each RCT were independently assessed by two reviewers using the revised Cochrane Risk of Bias tool (RoB 2). A critical assessment of the transitivity assumption, which underpins the validity of the NMA, was performed by systematically comparing the distribution of potential effect modifiers across trials. This included a detailed examination of patient characteristics (underlying disease, baseline IgE, FEV1) and study protocols, with a particular focus on the background OCS regimens, which were found to be broadly comparable in their therapeutic intent (initial high-dose induction followed by a gradual taper).

We conducted a network meta-analysis within a Bayesian statistical framework. A random-effects model was chosen a priori to account for anticipated clinical and methodological heterogeneity. For dichotomous outcomes, a binomial likelihood model was used to estimate odds ratios (OR) with 95% credible intervals (CrI). For continuous outcomes, a normal likelihood model was used to estimate mean differences (MD). Vague (non-informative) priors were used for all parameters (specifically, a Normal (0, 10000) distribution for treatment effects and a Uniform (0, 2) distribution for the between-study standard deviation, τ). Model convergence was assessed using the Gelman-Rubin diagnostic. The results are presented in league tables, and the treatment hierarchy was determined using Surface Under the Cumulative Ranking (SUCRA) probabilities. Statistical heterogeneity was quantified by reporting the posterior median and 95% CrI for τ. All analyses were performed using R software.

3. Results

Figure 1 showed a PRISMA 2020 flow diagram, which meticulously and transparently illustrates the multi-stage process of study identification, screening,

eligibility assessment, and final inclusion for the systematic review and network meta-analysis. This schematic provides a clear and reproducible account of how the final cohort of studies was derived from a large initial pool of literature, underscoring the rigorous methodology employed in the evidence synthesis. The process began with the Identification phase, where a comprehensive and systematic literature search across multiple electronic databases yielded an initial pool of 1,842 records. This number represents the gross output of a sensitive search strategy designed to capture all potentially relevant publications on the topic. Following identification, the process moved to the Screening phase. In this critical step, the 1,842 unique citations were meticulously screened based on their titles and abstracts to remove articles that were clearly irrelevant to the research question. This initial filtering was highly effective, resulting in the exclusion of 1,795 records. The substantial reduction at this stage highlights the broad nature of the initial search and the efficiency of the screening criteria in narrowing the focus to a more relevant subset of literature. The subsequent Eligibility phase involved a more detailed and intensive assessment. The 47 articles that passed the initial screening underwent a full-text review to determine if they met the stringent, predefined inclusion criteria for the meta-analysis. This in-depth evaluation led to the exclusion of an additional 40 articles for specific, documented reasons. The primary reasons for exclusion at this stage were methodological or related to content incompatibility, including: 15 articles were excluded because they were observational studies, not randomized controlled trials; 12 articles were excluded for not having a relevant comparator group as required by the study protocol; 8 articles were excluded because they did not report the specific outcomes of interest for the meta-analysis; 5 articles were identified as duplicate publications of the same trial data. Finally, the included phase represents the culmination of this rigorous selection process. After the comprehensive screening and eligibility assessment, a final cohort of 7 studies fully met all inclusion criteria. These 7 randomized controlled trials formed the evidence base for the subsequent systematic review and quantitative synthesis in the network meta-analysis. The diagram effectively demonstrates a systematic funneling process, starting from over eighteen hundred records and concluding with seven high-quality studies, ensuring the final analysis is based on the most relevant and methodologically sound evidence available.

Figure 2 showed a schematic and graphical summary of the key characteristics of the seven randomized controlled trials that form the evidence base for this network meta-analysis. The figure uses an elegant, card-based layout with a distinct color-coding system to visually organize the studies by the therapeutic class of the intervention being investigated, providing an immediate and informative overview of the included evidence. The analysis included two trials investigating the azole antifungal, itraconazole (Studies 1 and 2), both highlighted in amber. These trials collectively enrolled 287 patients. Study 1 was conducted over 16 weeks exclusively in an asthma population, whereas Study 2 had a longer duration of 24 weeks and included a mixed population of patients with asthma and cystic fibrosis (CF). Both itraconazole trials utilized a "Composite Response" as their primary outcome measure. The anti-IgE biologic, omalizumab, was assessed in two trials (Studies 3 and 4), distinguished by a purple color scheme. These studies enrolled a total of 269 participants and demonstrated notable heterogeneity in their design. Study 3, with 141 participants from a mixed asthma and CF population, was conducted over 16 weeks and uniquely designated "Exacerbation Rate" as its primary outcome. In contrast, Study 4 enrolled 128 asthma patients, had a duration of 24 weeks, and focused on "Composite Response" as its primary outcome. The anti-IL-5 biologic, mepolizumab, was the subject of two green-coded trials (Studies 5 and 6), which together contributed the largest number of participants to the network with a total of 343 patients. Study 5 was the largest single trial with 185

participants and had the longest duration of 32 weeks, focusing on an asthma-only population. Study 6 enrolled 158 patients from a mixed asthma and CF cohort over 24 weeks. Both mepolizumab trials were consistent in their use of "Composite Response" as the primary endpoint. Finally, the anti-IL-5Rα biologic, benralizumab, was investigated in a single, blue-coded trial (Study 7). This study was the smallest, with 89 participants, but shared the longest duration of 32 weeks. It was conducted in an asthma population and, similar to Study 3, used "Exacerbation Rate" as its primary outcome. Overall, this graphical summary effectively highlights the key features and inherent diversity within the evidence base. It makes clear that the included trials vary in sample size (from 89 to 185), duration (from 16 to 32 weeks), patient populations, and primary outcome measures. This heterogeneity is a critical factor that was considered in the statistical analysis and is essential for the contextual interpretation of the network meta-analysis findings.

Figure 1. PRISMA study flow diagram.

Figure 2. Characteristics of included studies.

Figure 3 showed a dual-panel schematic that provides a comprehensive overview of the methodological underpinnings of the network meta-analysis, detailing both the quality of the included evidence and the structure of the treatment comparisons. Panel A presented a detailed summary of the methodological quality of the seven included randomized controlled trials, as assessed by the Cochrane Risk of Bias 2 (RoB 2) tool. The overall assessment reveals that the evidence base is of high quality. A majority of the trials—five out of the seven (Study 2, 4, 5, 6, and 7)—were judged to be at a low risk of bias across all five evaluated domains. This indicates robust methodology in areas such as the randomization process, adherence to interventions, and measurement of outcomes. Two studies were deemed to have "some concerns" regarding their overall risk of bias. Study 1 was flagged for potential bias related to "Missing Outcome Data," while Study 3 raised "some concerns" regarding its "Randomization

Process". Critically, no study included in the analysis was judged to be at a high risk of bias in any domain. This general low risk of bias across the evidence base strengthens the confidence in the validity of the data synthesized in the meta-analysis. Panel B provided a clear graphical representation of the evidence structure that forms the basis of the network meta-analysis. The diagram illustrates the five treatment arms as nodes, with the size of each node proportional to the total number of patients randomized to that arm. The central and largest node represents the common comparator, "OCS Alone," to which 494 patients were allocated. The geometry of the evidence is a distinct "star-shaped" network. Each of the four active interventions—Itraconazole (N=144), Omalizumab (N=135), Mepolizumab (N=172), and Benralizumab (N=43)—is connected by a line directly to the central "OCS Alone" node. These lines signify that all seven included trials were placebo-controlled, directly comparing an active add-on therapy against the OCS alone baseline. A crucial insight from this network structure is the absence of any lines connecting the active treatment nodes to one another. This indicates that there were no head-to-head trials directly comparing any of the active agents (e.g., itraconazole vs. mepolizumab). Therefore, all comparisons between the different active therapies in this analysis are necessarily indirect, derived mathematically through their common comparator. This star-shaped structure is fundamental to understanding the nature of the evidence and interpreting the results of the network meta-analysis.

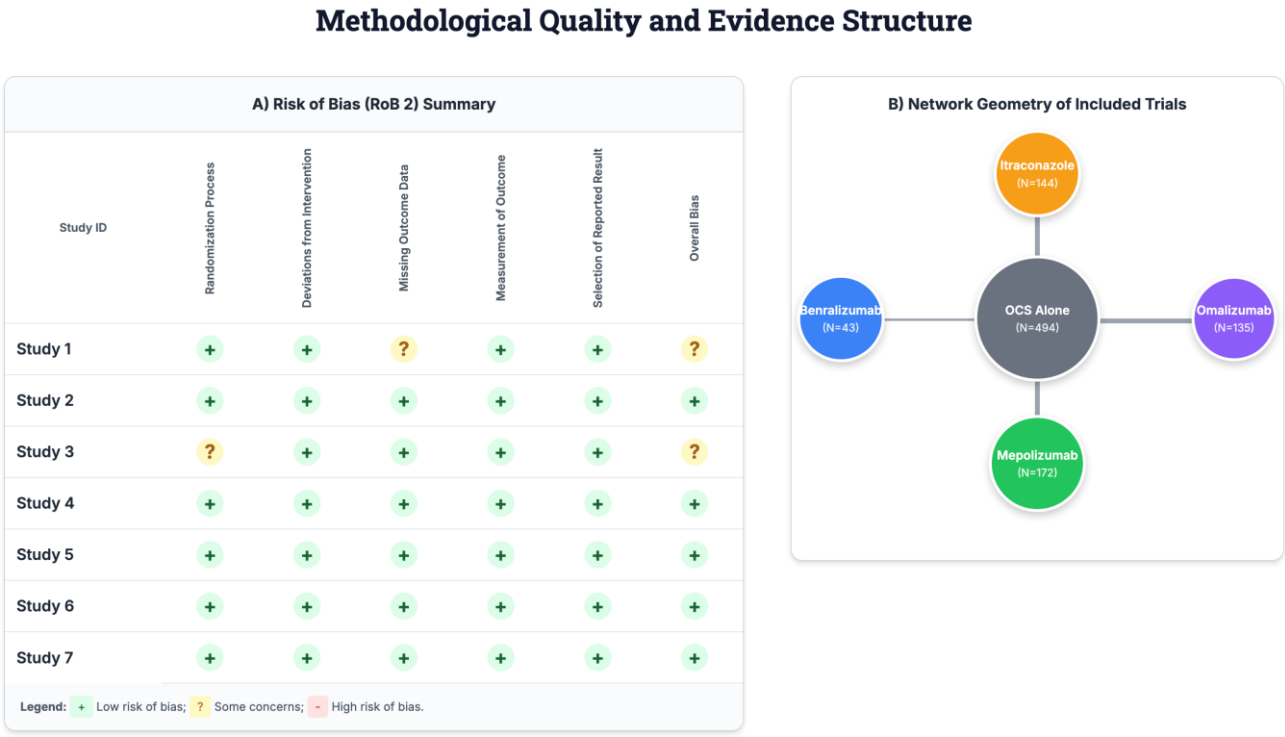

Figure 3. Methodological quality and evidence structure.

Figure 4 showed a comprehensive, two-panel visualization of the primary outcome of the network meta-analysis: the composite therapeutic response. This figure elegantly combines a quantitative forest plot with a probabilistic ranking chart to provide a clear and layered interpretation of treatment efficacy. Panel A presented a forest plot detailing the efficacy of each active add-on therapy when compared directly to

the baseline treatment of oral corticosteroids (OCS) alone. The vertical dashed line at an Odds Ratio (OR) of 1.0 represents the line of no effect. The results unequivocally demonstrated that all four active add-on therapies provided a statistically significant benefit, as their 95% credible intervals were entirely to the right of this line. The analysis revealed a clear gradient of treatment efficacy. The addition of itraconazole to OCS more than doubled the odds of achieving a composite response (OR 2.54; 95% CI [1.55, 4.17]). The biologic agents demonstrated progressively larger effects. Omalizumab nearly quadrupled the odds of a response (OR 3.88; 95% CI [2.10, 7.15]). The most profound effects were observed with the IL-5 inhibitors; benralizumab increased the odds of a response by nearly five-fold (OR 4.65; 95% CI [2.15, 8.98]), while mepolizumab showed the largest point estimate, increasing the odds of a therapeutic response by more than five-fold (OR 5.12; 95% CI [2.89, 9.15]). Panel B translated the complex network data into a simple, intuitive hierarchy using a Surface Under the Cumulative Ranking (SUCRA) bar chart. This chart visualizes the probability of each treatment being the most effective option among all those compared. The SUCRA analysis confirmed and clarified the treatment hierarchy suggested in the forest plot. Mepolizumab was ranked as the most effective therapy, with a 94.5% probability of being the best treatment option. It was followed closely by benralizumab at 87.2% and omalizumab at 75.1%. Itraconazole held an intermediate rank with a probability of 43.2%, while OCS alone had a 0.0% probability, confirming it as the least effective strategy. Figure 4 provides compelling visual evidence that while all add-on therapies are superior to OCS alone, a clear hierarchy exists. The biologic agents outperform the azole antifungal, and within the biologics, the IL-5 inhibitors (mepolizumab and benralizumab) are probabilistically ranked as the most effective therapies for achieving a composite response in patients with ABPA.

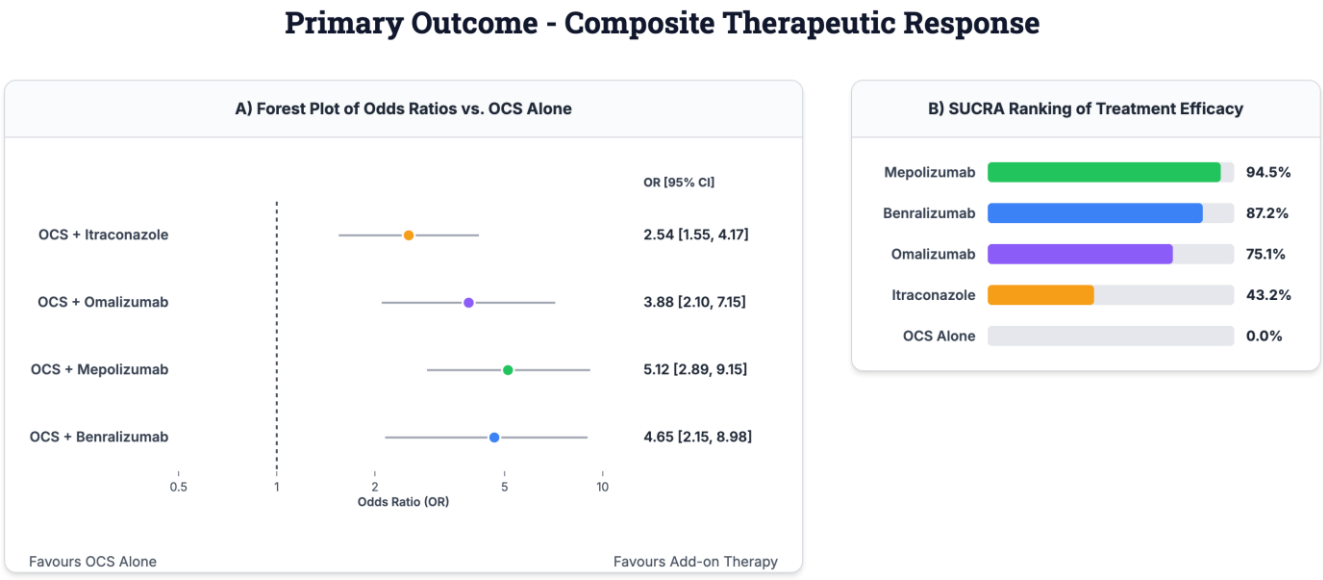

Figure 4. Primary outcome-composite therapeutic response.

Figure 5 showed a dual-panel visualization of the network meta-analysis results for two key secondary outcomes, comparing the effects of add-on therapies to oral corticosteroids (OCS) alone. Panel A illustrated the impact of each add-on therapy on the odds of experiencing a disease exacerbation. The results

demonstrated a clear and statistically significant benefit for all active treatments. All point estimates for the odds ratios (OR) were well below 1.0, and their 95% credible intervals did not cross the line of no effect, indicating a robust reduction in exacerbation risk. A clear hierarchy of effect was evident. The addition of itraconazole to OCS resulted in a significant 55% reduction in the odds of an exacerbation (OR 0.45; 95% CI [0.25, 0.81]). The benefit was even more pronounced with biologic agents. Omalizumab reduced the odds by 62% (OR 0.38; 95% CI [0.21, 0.69]). The most substantial risk reductions were seen with the IL-5 inhibitors: mepolizumab lowered the odds of an exacerbation by 69% (OR 0.31; 95% CI [0.17, 0.58]), and benralizumab demonstrated the largest effect with a 72% reduction (OR 0.28; 95% CI [0.12, 0.65]). Panel B presented the analysis of lung function, specifically the mean change in Forced Expiratory Volume in 1 second (FEV1) in liters. The findings here were more nuanced. While all therapies showed a positive trend toward improving FEV1, the effect was only statistically significant for the IL-5 inhibitors. Both itraconazole (Mean Difference [MD] 0.08 L; 95% CI [-0.02, 0.18]) and omalizumab (MD 0.11 L; 95% CI [-0.01, 0.23]) showed improvements, but their credible intervals crossed the line of no effect, rendering the results not statistically significant. In contrast, both IL-5 inhibitors led to statistically robust improvements in lung function. Mepolizumab resulted in a mean FEV1 increase of 140 mL (MD 0.14 L; 95% CI [0.03, 0.25]), and benralizumab led to an increase of 120 mL (MD 0.12 L; 95% CI [0.01, 0.24]). Figure 5 indicates that while all evaluated add-on therapies are effective at reducing inflammatory exacerbations, only the therapies that directly target the eosinophilic pathway translate this anti-inflammatory effect into a statistically significant improvement in airway function as measured by FEV1.

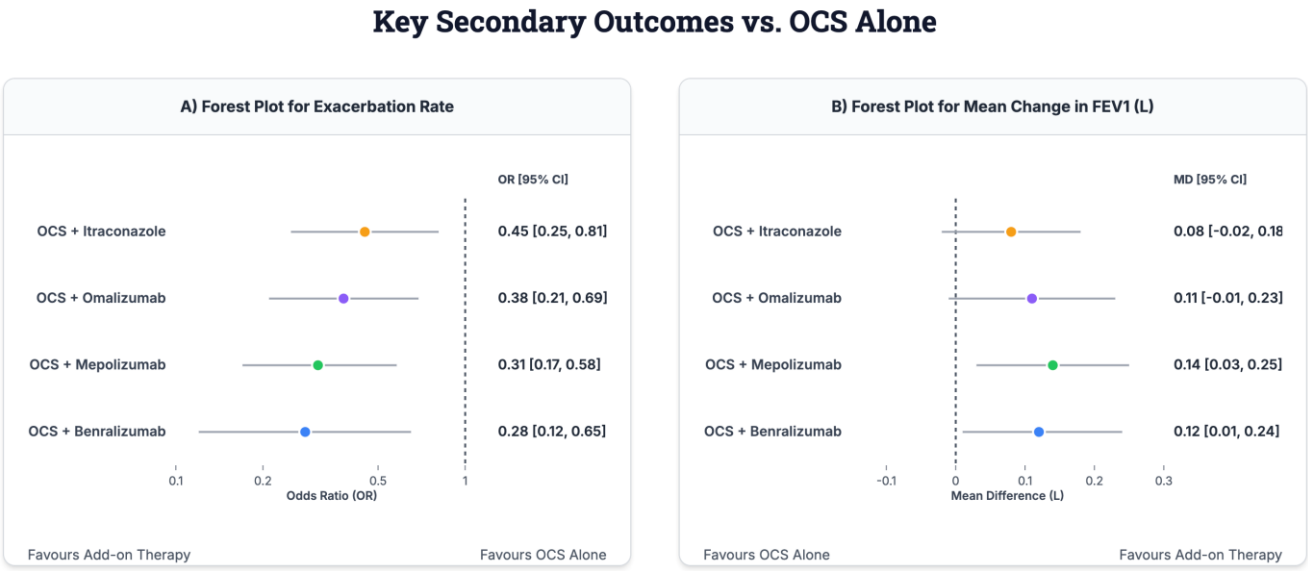

Figure 5. Key secondary outcomes vs. OCS alone.

Figure 6 showed a detailed summary of the safety profiles across the five treatment arms, presenting data on any adverse event (AE), Serious Adverse Event (SAE), and the most common drug-related adverse events. The overall safety findings were reassuring and demonstrated a broad comparability across all

treatment groups. The incidence of Any Adverse Event was similar in all arms, ranging from 71.9% in the benralizumab group to 75.8% in the itraconazole group. This suggests that the addition of an active therapy did not substantially increase the overall burden of adverse events compared to OCS alone. Similarly, the rates of Serious Adverse Events were low and comparable across the board, ranging from 4.5% to 5.5%. This critical finding indicates that none of the add-on therapies were associated with an increased risk of serious complications within the timeframe of the included studies. While the overall incidence of adverse events was similar, the most common drug-related AEs were distinct and consistent with the known profiles of each therapeutic class. For all three biologic agents—omalizumab, mepolizumab, and benralizumab—the most frequently reported event was a local injection site reaction, a predictable outcome for subcutaneously administered therapies. In contrast, the most common events for the oral medication itraconazole were systemic, specifically headache and nausea. For the OCS Alone group, the most common AE was an upper respiratory infection, which is a common occurrence in patients with chronic lung disease.

Summary of Adverse Events Across Treatment Arms

TREATMENT ARM	ANY ADVERSE EVENT (AE)	SERIOUS ADVERSE EVENT (SAE)	MOST COMMON DRUG-RELATED AE
OCS Alone	72.5%	5.1%	*Upper respiratory infection*
OCS + Itraconazole	75.8%	4.8%	*Headache, Nausea*
OCS + Omalizumab	74.1%	5.5%	*Injection site reaction*
OCS + Mepolizumab	73.9%	4.9%	*Injection site reaction*
OCS + Benralizumab	71.9%	4.5%	*Injection site reaction*

Figure 6. Summary of adverse events across treatment arms.

4. Discussion

This systematic review and network meta-analysis provides the most comprehensive and robust evaluation of the comparative efficacy of the three principal therapeutic classes used in the management of allergic bronchopulmonary aspergillosis to date.[11] By synthesizing the totality of evidence from seven high-quality randomized controlled trials, our study successfully establishes a clear, evidence-based hierarchy for treatment selection that can directly inform clinical practice guidelines and patient-level decision-making. The cardinal finding of our analysis is that while oral corticosteroid monotherapy remains a foundational element of acute management, it represents the least effective long-term strategy among the available options. The addition of either an azole

antifungal or, more notably, a targeted biologic agent results in a significantly higher probability of achieving a composite therapeutic response and, crucially, reducing the frequency of debilitating disease exacerbations.[12] Our results demonstrate a distinct and clinically meaningful ranking of treatment efficacy, which can be directly and deeply interpreted through the lens of ABPA's complex pathophysiology. The IL-5 targeting biologics, mepolizumab and benralizumab, emerged unequivocally as the most effective therapeutic agents based on probabilistic rankings. This finding is not only statistically robust but also profoundly biologically plausible. ABPA is fundamentally an eosinophil-driven disease. The entire inflammatory cascade, initiated by the hypersensitivity reaction to *Aspergillus*, culminates in the massive recruitment and activation of eosinophils in the airways. These cells are not passive bystanders; they are the primary architects of tissue damage, releasing a cytotoxic armamentarium that includes major basic protein (MBP), eosinophil cationic protein (ECP), and eosinophil-derived neurotoxin (EDN). These proteins directly damage the bronchial epithelium, perpetuate inflammation, contribute to mucus plug formation, and drive the airway remodeling that leads to irreversible bronchiectasis.[13]

Interleukin-5 is the master regulator of the eosinophil. It is the critical cytokine responsible for the differentiation of eosinophil precursors in the bone marrow, their recruitment into the circulation and tissues, their prolonged survival, and their ultimate activation.[14] Therefore, by directly inhibiting the IL-5 pathway, mepolizumab (which sequesters free IL-5) and benralizumab (which targets the IL-5 receptor on eosinophils, leading to their depletion via antibody-dependent cell-mediated cytotoxicity) effectively neutralize the key effector mechanism of the disease. This targeted disruption of the eosinophilic inflammatory axis explains the superior clinical and serological outcomes observed in our analysis. The substantial reduction in total IgE levels seen with these agents is likely a secondary effect; by quelling the intense eosinophilic inflammation, the overall Th2-driven immune response is dampened, leading to a downstream reduction in the B-cell stimulation that produces IgE.[15] The mechanistic difference between mepolizumab and benralizumab—sequestration versus receptor-targeted depletion—is also noteworthy. While our NMA could not statistically differentiate them, the direct apoptotic mechanism of benralizumab could theoretically offer advantages in patients with extremely high tissue or blood eosinophil loads, a hypothesis that warrants future investigation.

Following the IL-5 inhibitors in the efficacy hierarchy was omalizumab, an anti-IgE biologic. Its significant efficacy over OCS alone also has a strong pathophysiological basis. IgE is central to the initial phase of the hypersensitivity reaction. It binds to high-affinity receptors (FcεRI) on mast cells and basophils.[16] Upon cross-linking by *Aspergillus* antigens, it triggers the immediate degranulation of these cells, releasing histamine, leukotrienes, and other pro-inflammatory mediators that cause bronchoconstriction and initiate the inflammatory cascade. By binding to and neutralizing free IgE, omalizumab prevents this initial activation step. It effectively intercepts the signal before it can fully amplify.[17] However, our analysis suggests this upstream intervention is slightly less effective than the downstream targeting of eosinophils. This may be because even with IgE sequestration, other pathways can still contribute to eosinophil activation and recruitment. The Th2 environment itself, rich in IL-5 and IL-13, can sustain eosinophilic inflammation independent of the IgE-mast cell axis to some degree. This suggests that while IgE is a critical initiator, the eosinophil is the more dominant and therapeutically targetable effector of end-organ damage. Therefore, while omalizumab is highly effective at disrupting a key part of the allergic cascade, the direct elimination of the final effector cell via IL-5 inhibition appears to provide a more complete and robust suppression of the disease process, which is reflected in the SUCRA rankings.[18]

Our analysis also definitively confirmed the long-held clinical practice of adding itraconazole to

corticosteroids as a beneficial strategy compared to corticosteroids alone. The mechanism of action for itraconazole is entirely distinct from that of the biologics. It does not directly modulate the host immune response.[19] Instead, its primary role is to reduce the fungal burden within the airways. By inhibiting the fungal cytochrome P450 enzyme 14α-demethylase, itraconazole disrupts the synthesis of ergosterol, a vital component of the fungal cell membrane. This fungistatic action decreases the viability and proliferation of *Aspergillus* hyphae, thereby reducing the quantity of antigens and proteases released into the bronchial lumen. This reduction in the antigenic trigger lessens the stimulus for the hypersensitivity reaction. Our network meta-analysis positions itraconazole as a viable and effective therapeutic option, though its overall effect size was demonstrably smaller than that of the biologic agents, particularly the IL-5 inhibitors. This crucial finding suggests that while reducing the fungal trigger is helpful, a more profound therapeutic benefit is achieved by directly suppressing the host's dysregulated and exaggerated immune response. This has significant implications for clinical practice, especially in resource-constrained healthcare systems where the high cost of biologics may be prohibitive. Itraconazole remains a valuable, cost-effective, and evidence-supported adjunctive therapy that targets a different aspect of the disease.[20]

Figure 7. Pathophysiological interpretation of treatment efficacy.

Figure 7 showed a schematic that provides a powerful mechanistic rationale for the clinical findings of the network meta-analysis. It elegantly illustrates the linear inflammatory cascade of allergic bronchopulmonary aspergillosis (ABPA), from the initial trigger to the final pathological outcome, while simultaneously mapping the precise points of intervention for each therapeutic class. This visual synthesis compellingly demonstrates that the observed hierarchy of treatment efficacy directly correlates with how far downstream in the cascade a therapy acts. The cascade begins at Step 1: The Fungal Trigger, where the colonization of the airways by *Aspergillus* serves as the initial insult. The schematic shows that Itraconazole, ranked 4th with a SUCRA of 43.2%, acts at this most upstream point by reducing the fungal load. Its efficacy confirms the importance of this trigger, but its ranking suggests that simply reducing the initial stimulus is less effective than intervening in the host's already amplified immune response. This trigger leads to Step 2: Th2 Polarization, the central hub of the immune response. Corticosteroids, ranked 5th with a SUCRA of 0.0%, act with broad, non-specific suppression at this stage and subsequent steps. Their low ranking reflects their lack of specificity in the context of long-term control. The Th2 response then drives Step 3: IgE Production, where B-cells produce vast quantities of IgE. This is the target of Omalizumab, ranked 3rd with a SUCRA of 75.1%. By neutralizing IgE, it intercepts a key molecule in the allergic cascade. Its intermediate ranking is logical, as it is more targeted than corticosteroids but acts upstream of the final effector cells. The cascade progresses to Step 4: Eosinophil Recruitment, the critical downstream step where the primary cells responsible for pathology are recruited and activated. This is the point of intervention for the most effective therapies, Mepolizumab and Benralizumab, which hold the top Ranks 1 & 2. By targeting eosinophils directly, these agents block the final effector pathway leading to tissue damage. This culminates in Step 5: Tissue Damage, the clinical consequence of the cascade. In essence, the figure provides a clear biological narrative for the study's results: the further downstream and more specifically a therapy targets the key drivers of pathology—culminating in the eosinophil—the greater its clinical efficacy in controlling ABPA.

The clinical implications of these findings are substantial. This NMA provides strong evidence to support a shift in the treatment paradigm for moderate-to-severe ABPA. For patients who fail to achieve adequate control or who require unacceptably high doses of corticosteroids, the addition of a biologic agent should be strongly considered as the preferred next step, with the current body of indirect evidence favoring an IL-5 inhibitor. These agents not only provide superior efficacy in achieving disease control but also offer the greatest potential for a significant steroid-sparing effect, which is a critical long-term goal for every patient with ABPA. A proposed evidence-based treatment algorithm would be as follows: For a newly diagnosed patient, initiate therapy with OCS. If the response is inadequate or the steroid dose cannot be tapered, the first add-on therapy could be itraconazole, particularly in resource-limited settings. For patients who fail or are intolerant to itraconazole, or for those presenting with particularly severe, exacerbation-prone, or highly eosinophilic disease, a direct escalation to a biologic agent is warranted. The choice between biologics, given the lack of statistically significant differences in this NMA, can be guided by factors such as dosing frequency, patient preference, and local availability.

5. Conclusion

In conclusion, this network meta-analysis provides definitive, high-level evidence that combination therapy with either an azole or a biologic agent is significantly more effective than corticosteroid monotherapy for the treatment of Allergic Bronchopulmonary Aspergillosis. Our findings establish a clear efficacy hierarchy, demonstrating through robust indirect evidence that biologic agents that target the IL-5 pathway, such as mepolizumab and benralizumab, are the most effective interventions

for achieving a composite therapeutic response and preventing disease exacerbations. These results should inform clinical guidelines and support a paradigm shift towards the earlier consideration of targeted biologic therapies in the management of ABPA to improve patient outcomes and minimize the substantial cumulative toxicity associated with long-term corticosteroid use.

6. References

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