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REVIEW

Exploring Human Use of Monoclonal Antibodies Against Critical Bacteria: A Scoping Review of Clinical Trials

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ABSTRACT

***Introduction*:** The global spread of multidrug-resistant organisms (MDROs), particularly the World Health Organization (WHO) priority pathogens, poses a major challenge to infection treatment, necessitating alternative therapeutic strategies. Monoclonal antibodies (mAbs) have emerged as a potential approach. This review evaluates the clinical efficacy, safety, and limitations of mAbs targeting critical bacterial pathogens, analyzing factors influencing therapeutic outcomes, and proposing strategies to optimize their clinical application.

***Methods*:** A comprehensive analysis of clinical trials investigating antibacterial mAbs was conducted. The review assessed key factors influencing therapeutic outcomes, including trial design, patient heterogeneity, and pharmacokinetics (PK). Comparative analysis was performed to examine differences in efficacy, safety, and limitations across studies. A structured risk of bias assessment was performed using Cochrane Methods' tools.

Marco Piscaglia and Giovanni Scaglione share first authorship.

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Results: Owing to the low number of studies against MDROs, all trials about mAbs targeting *Staphylococcus aureus* (SA) and *Pseudomonas aeruginosa* (PA) were included, disregarding resistance profiles. Generally, clinical trials evaluating antibacterial mAbs have shown preliminary evidence. For PA, panobacumab exhibited a favorable safety profile but lacked clear clinical benefits, showing a good survival rate but in a small uncontrolled trial. Rivabazumab reduced bacterial colonization, but did not significantly lower pneumonia incidence. Gremubamab was well tolerated but failed to meet efficacy endpoints. For SA, tosatoxumab and suvratoxumab failed to show statistical significance but may have potential benefits for pneumonia, although phase III trials are needed.
Conclusions: Inconsistent efficacy may stem from complex host–pathogen interactions, biofilm formation, and variations in patient immune status. Future trials should investigate early mAb administration, stratified patient selection, and standardized antibiotic coadministration, poorly addressed thus far. Optimized dosing and mAb combination regimens are promising yet unexplored paths, while high production costs and regulatory issues remain a significant barrier.

Keywords: Monoclonal antibodies; Multidrug-resistant; Antimicrobial resistance; Novel treatments

Key Summary Points

The increasing global threat of multidrug-resistant organisms (MDROs), mostly sustained by pathogens included in the World Health Organization (WHO) bacterial priority pathogens list, poses serious treatment challenges and an economic burden, driving the exploration of alternative therapeutic strategies, such as monoclonal antibodies (mAbs), to address an unmet clinical need.

The study mapped the existing clinical trials on the efficacy and safety of mAbs targeting key WHO priority pathogens, specifically *Staphylococcus aureus* (SA) and *Pseudomonas aeruginosa* (PA), exploring reported outcomes, pharmacokinetics (PKs), and safety profiles.

In this scoping review, 18 eligible papers were included, 11 via a predefined search strategy and 7 manually added via backward snowballing, highlighting consistent safety but mixed results regarding the effectiveness of mAbs in clinical trials.

Inconsistent efficacy may be a result of multiple factors, including trial limitations, patient heterogeneity, and pathogen diversity

mAbs could be a promising novel therapeutic approach against critical bacteria. Yet, many challenges have to be overcome in future studies in order to enhance the informativity and reproducibility of clinical trials on these agents.

INTRODUCTION

Antimicrobial resistance (AMR) is significantly increasing worldwide [1]. This growing trend is largely sustained by bacterial pathogens included in the critical and high-priority groups of the World Health Organization (WHO) bacterial priority pathogens list of 2024 [2]. While key drivers of AMR include overuse of antibiotics in healthcare and agriculture and inadequate infection control, effective measures to mitigate its growing trend also involve the development of novel treatments [3]. Since novel antibiotic classes and combinations modifying existing chemical structures have not been sufficient to keep up with the evolving resistance, there is a current urgent need for innovative therapeutic strategies [4]. Several different promising non-antibiotic antibacterial approaches have been tested over the last years. They include bacteriophage therapy, which employs viruses to specifically target and lyse bacterial pathogens, and antimicrobial peptides that disrupt bacterial membranes. Moreover, nanoparticles offer

targeted delivery of antimicrobial agents, enhancing efficacy and reducing resistance. Antivirulence agents work by inhibiting bacterial pathogenic mechanisms without killing the bacteria, thereby reducing selective pressure for resistance. In addition, CRISPR-Cas9 technology has been explored to selectively target and disrupt bacterial genomes [5]. Among these strategies, monoclonal antibodies (mAbs) have also been developed as potential therapies against bacterial pathogens, including high-mortality pathogens and multidrug-resistant organisms (MDROs), offering several advantages. These agents act through diverse mechanisms, including the neutralization of bacterial virulence factors (e.g., toxins and secretion system proteins) and the targeting of structural components such as surface adhesins or polysaccharides. This specificity of action reduces off-target effects, minimizes toxicity compared with traditional antibiotics, and helps preserve host microbiota, potentially preventing the spread of difficult-to-treat organisms [6]. In addition, in immunocompromised patients, mAbs might provide passive protection, overcoming deficiencies in immune responses [7]. Finally, mAbs generally have longer half-lives, requiring fewer doses, and possibly improving patient compliance [8].

Along with these potential advantages, mAbs application against critical bacteria, such as *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species (ESKAPE) pathogens, faced some challenges, and preclinical models often failed to predict clinical outcomes [9]. Furthermore, high production costs restrict accessibility, particularly in low-resource settings [10] and immune responses such as antidrug antibodies (ADA) may reduce efficacy and increase adverse effects [11].

As no comprehensive summary of this topic is currently available, we wanted to explore the use of mAbs against critical bacteria, focusing specifically on clinical studies in humans rather than in vitro research. By mapping existing human studies, we aimed to provide a clearer overview of the preventive and therapeutic usage, safety and pharmacokinetic (PK) parameters, and potential limitations of mAbs directed against WHO priority bacteria in clinical settings.

METHODS

This scoping review partially follows the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement for the search strategy [12]. The PRISMA checklist for this scoping review is provided in the Supplementary Materials (Supplementary Table S1). The protocol was registered on OSF (https://doi.org/10.17605/OSF.IO/4N5Y2).

Information Sources

Data were collected screening the major scientific databases (Medline, Embase, Web of Science, Scopus, Cochrane), up to March 2024. Research strategy included terms such as "monoclonal", "antibodies", "immunotherapy", "bacteria", "resistance". The full list of terms and the complete research strategy is presented in the Supplementary Materials.

Eligibility Criteria and Study Selection

With this scoping review, we wanted to explore the administration of mAbs active against MDROs in clinical and research settings. However, despite the initial eligibility criteria being focused on trials specifically targeting MDROs, we decided to revise the search strategy owing to the paucity of results and the characteristics of the studies that underwent full-text screening. In particular, our definitive search strategy finally included articles that met the criteria of use of mAbs against gram-negative and gram-positive bacteria according to the bacterial priority pathogen list by the World Health Organization (WHO) in humans [2], disregarding their resistance profile. This list includes pathogens such as drug-resistant *Enterobacterales*, *Enterococci*, *Streptococci*, *Staphylococcus aureus* (SA), *P. aeruginosa* (PA), *A. baumannii*, *Salmonella* spp., *Shigella* spp., *Haemophilus influenzae*, and *Neisseria* spp.

Eligible studies included prospective interventional studies, both comparative and non-comparative. Interventions consisted of mAbs administered for either prophylactic or therapeutic purposes. Additional inclusion criteria

required articles to be written in English and published in peer-reviewed journals. Since we wanted to explore the clinical use of mAbs in humans against first MDROs and then critical/priority pathogens, disregarding resistance profiles, we proceeded to exclude all studies non-informative on this topic. Exclusion criteria at the title and abstract screening stage were: (1) in vitro studies (2) animal model research, (3) noninterventional studies (observational studies, letters, editorials), (4) studies on nonbacterial pathogens (e.g., viruses, fungi, parasites, and mycobacteria); (5) studies on mAbs against bacterial pathogens without in vivo administration of the compound to treat or prevent a bacterial infection; (6) studies not regarding mAbs; and (7) grey literature (such as conference posters or abstracts). Furthermore, all duplicate studies were removed.

In the full-text screening stage, we proceeded to exclude all studies with literature review designs, studies not actually describing mAb administration in human subjects, or not focusing on MDROs, particularly extended-spectrum beta-lactamases producing *Enterobacterales*, carbapenemase-producing *Enterobacterales*, PA, *A. baumannii*, vancomycin-resistant *Enterococci*, and methicillin-resistant SA. However, five studies with limited sample sizes reported on resistance profiles. Therefore, we revised the search strategy, leaving the title/abstract screening criteria unmodified, and abandoned the MDRO selection criteria at the full-text screening stage in favor of the WHO critical pathogens list criteria, which meant excluding studies focusing, for example, on mAb administration for *Clostridioides difficile*, *Helicobacter pylori*, *Francisella tularensis*, or *Bacillus anthracis*, while studies focusing on any WHO critical pathogen, according to its 2024 version, were included, disregarding their resistance profile.

In addition to database searches, we applied a systematic backward snowballing strategy, which means that: (1) two reviewers (M.P. and G.S.) independently screened the reference lists of all included studies, (2) we extracted and screened titles and abstracts of potentially relevant citations using the same eligibility criteria applied to database searches, and (3) we applied a snowballing process in an iterative way. Specifically, reference lists of newly included studies from snowballing were screened until no additional eligible studies were identified, and the number of additional studies identified through snowballing were tracked separately from database results. Finally, any disagreements during snowballing screening were resolved through discussion or consultation with a third reviewer (E.P.).

The study selection process was conducted using the Rayyan software (http://rayyan.qcri.org/). Five reviewers (M.P., G.S., F.B., F.Bo., and C.G.) independently screened the titles and abstracts of all records to determine eligibility for full-text review. Any disagreements were resolved through consultation with two additional reviewers (E.P. and M.C.). The included articles were thoroughly reviewed in full by a reviewer different from the one who performed the initial screening.

Data Extraction

After the screening phase, data were independently extracted by five reviewers (M.P., G.S., F.B., F.Bo., and C.G.), and all results were thoroughly cross-checked for accuracy. The extracted data included descriptive information such as study design, setting, population, study aims, primary and secondary outcomes. The data-extraction matrix was created in Microsoft Excel to capture key study characteristics (e.g., author, year, pathogen targeted, mAb agent, trial phase, population, intervention details, outcome measures, and safety/adverse events). Prior to full extraction, two reviewers (G.S. and F.Bo.) independently piloted the template on a random sample of five included studies (≈20% of the initial corpus). The template was then shared with the other coauthors, and when discrepancies were found, a third reviewer (C.G.) settled them.

Three review authors (M.P., G.S., and F.B.) independently assessed risk of bias using the Cochrane "risk of bias in randomized trials" tool (ROB2) for all safety and clinical efficacy outcomes separately (when data were provided) [13]. Differences between ROB2 assessments were discussed between G.S., F.B., and M.P., until consensus was reached, and discrepancies were

resolved. Only one phase I study did not have a comparator and was evaluated for clinical safety and efficacy separately with the risk of bias in nonrandomized studies - of interventions, version 2 (ROBINS-I V2) tool's seven items according to Cochrane Methods' guidelines [14, 15]. We assessed risk of bias in controlled trials using the following Cochrane ROB2 criteria: (1) bias arising from the randomization process; (2) bias owing to deviations from intended interventions; (3) bias owing to missing outcome data; (4) bias in measurement of the outcome; (5) bias in selection of the reported result. Figures and tables were obtained via the robvis visualization tool [16].

Ethical Approval

The protocol was registered on OSF (https://doi.org/10.17605/OSF.IO/4N5Y2). This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

We identified a total of 5016 records. Figure 1 presents the PRISMA flowchart, which illustrates the study selection process for this review. Of the 5016 studies, 1500 were excluded as duplicates. Screening was conducted on 3516 papers, leading to the exclusion of 3350. The full text of 166 articles was assessed, resulting in 11 studies meeting the inclusion criteria. An additional 7 studies were identified and manually added via reference list screening, bringing the total number of eligible papers to 18.

The included clinical trials focused exclusively on mAbs targeting PA and *Staphylococcus* spp. No trials focusing on Enterobacterales, Enterococci, or other gram-positive and gram-negative microorganisms included in the WHO priority pathogen list of 2024 were retrieved.

Of the included studies, only 5 out of 18 (27.8%) provided data on resistance mechanisms or documented resistance to one or more antimicrobial agents. In all five studies, antimicrobial resistance was only described in the baseline population characteristics, and no subgroup analyses on safety, efficacy, and PK outcomes were performed according to antimicrobial resistance profiles. Furthermore, none of these studies discussed the potential impact of the resistance profile on any considered outcome. Of the remaining 13 studies, 4 were phase I studies conducted on healthy volunteers, one study was only focusing on PA serotype but not on antimicrobial resistance, and the remaining 8 did not mention resistance profiles, mechanisms, or any other data potentially informing on the susceptibility to antimicrobial agents.

Given the paucity of studies, and the heterogeneity of their designs and outcomes, we present a narrative synthesis of articles that met the criteria of use of mAbs against gram-negative and gram-positive bacteria included in the WHO bacterial priority pathogen list, disregarding their resistance profile.

Monoclonal Antibodies (mAbs) Against *Pseudomonas aeruginosa* (Table 1)

Panobacumab (KBPA-101)

Panobacumab is a fully human immunoglobulin (Ig) M(κ) mAb targeting the O-polysaccharide of PA serotype O11 lipopolysaccharide, which accounts for approximately 20% of all PA isolates. It is designed to kill the bacterium by mediating complement-dependent opsonophagocytosis.

The clinical efficacy of panobacumab was evaluated in a phase II study in 18 critically ill patients with hospital-acquired PA (serotype O11) pneumonia (HAP), 15 of whom were affected by ventilator-associated pneumonia (VAP). In the intention-to-treat analysis of 17 patients, 14 out of 17 patients (82.4%) survived to day 30, and 11 out of 17 (64.7%) achieved clinical resolution, suggesting a potentially favorable efficacy profile despite the absence of a comparator arm. Relapses occurred in two patients, with an overall high cure rate. Antibiotic regimens were uncontrolled across patients

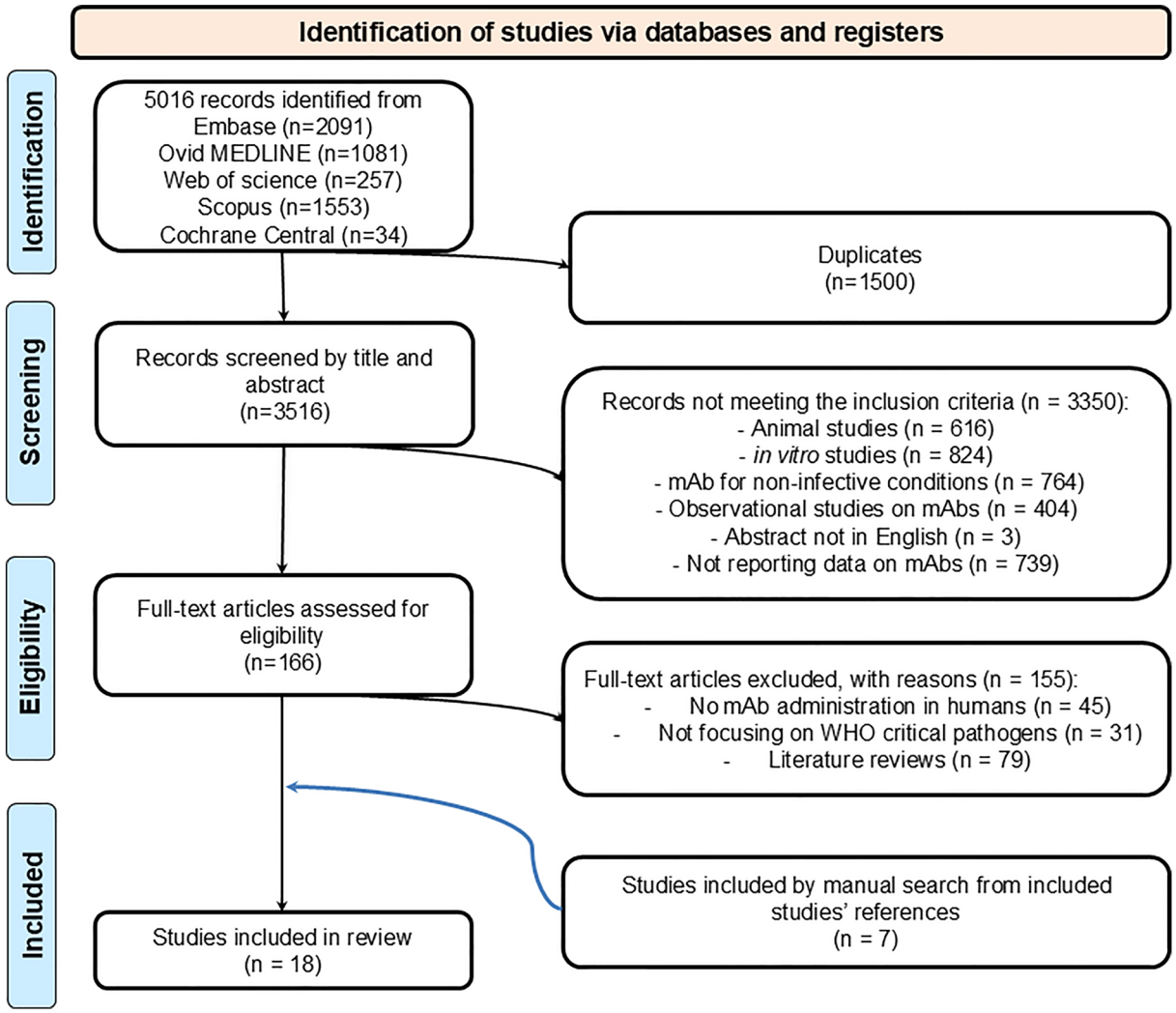

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart. *WHO* World Health Organization, *mAb/mAbs* monoclonal antibody/antibodies

and treatment was discontinued in three cases due to serious adverse events (SAEs), including one death. Overall, panobacumab was well tolerated, with no immunogenicity or significant systemic AEs reported [17].

Similar findings on drug safety were observed in a previous phase I study involving 32 healthy volunteers, with mild-to-moderate adverse events (AEs) in 25% of participants, no SAEs, and no anti-drug antibody (ADA) formation.

The same study assessed PK at escalating doses, with panobacumab exhibiting linear PK with a half-life of 70–95 h [17, 18].

Rivabazumab (KB001)

Rivabazumab is a recombinant, polyethylene glycol (PEG)ylated, engineered human Fab' fragment that targets the PcrV protein of PA, a key component of the type III secretion system (TTSS), which is involved in the virulence of PA. The TTSS enables the injection of exotoxins into eukaryotic cells, contributing to macrophage and neutrophil cytotoxicity. Owing to the lack of the Fc effector portion, rivabazumab acts as a TTSS inhibitory drug. The efficacy of rivabazumab was assessed in a randomized, double-blind, placebo-controlled phase IIA trial

Table 1 Monoclonal antibodies against *Pseudomonas aeruginosa*

Name and target	Phase I trials				Phase II–III trials				
	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Key findings	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Co-Atb	Key findings
Panobacumab (KBPA-101) LPS O-polysaccharide moiety of *PA* serotype IATS O11	Lazar, 2009	Dose escalation 24 (32) HV	Safety and PK Incidence of AEs PK parameters	Eight subjects experienced a total of nine AEs. No sAE reported. Most frequent AE: headache No ADA formation reported Linear PK across all doses. Mean half-life was between 70 h and 95 h	Lu, 2011	Open label CT 17 (18) ICU	Treatment of HAP/VAP Incidence of AEs Survival Clinical outcomes	Yes, not controlled	8/96 AEs potentially drug related. Three sAE reported, including one death. Most frequent AE: erythema Clinical outcome (ITT): resolution 11/17 (64.7%), recurrence 2/17 (11.7%), continuation 4/17 (23.5%) Overall patient survival at day 30 (ITT): 14/17 (82.4%)

Table 1 continued

Name and target	Phase I trials				Phase II–III trials				
	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Key findings	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Co-Atb	Key findings
Rivabazumab (KB001) *PA* PcrV protein	Milla, 2014	Dose escalation 18 (27) CF subjects	Safety, PK, immunogenicity, and PD Incidence of AEs PK parameters Symptoms and spirometry parameters *PA* density in sputum Inflammatory cytokines in sputum	Well-tolerated: no deaths or life-threatening adverse events. Most AEs and sAEs consistent with underlying CF Favorable PK and half-life of 11.9 days No significant differences in *PA* density, symptoms, or spirometry. At day 28 trend towards a dose-dependent reduction in sputum MPO, ILs, sputum neutrophil elastase and neutrophil counts versus placebo	François, 2012	Phase II RCT 27 (39) ICU	Prevention of PA pneumonia Incidence of Aes PK parameters Incidence of *PA* pneumonia	No	15/27 (55.5%) patients exposed to drug and 7/12 (58.3%) exposed to placebo reported at least one sAE. One mild AE deemed to be drug related. Most frequent AEs: transiently increased serum aminotransferase Favorable PK profile, with predictable penetration into respiratory secretions PA pneumonia incidence: 8/25 (32.0%) versus placebo 6/10 (60.0%)

Table 1 continued

Name and target	Phase I trials				Phase II–III trials				
	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Key findings	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Co-Atb	Key findings
					Jain, 2018	Phase III RCT 83 (169) CF subjects	Treatment of chronic *PA* infection in CF Time to need of antibiotics FEV_1 variations	Inhaled anti*PA* Atb	There was no statistical difference in time to need antibiotic between study drug and placebo groups (HR: 1.00, 95% CI 0.69, 1.45, $p = 0.995$) 3.2% increase in FEV_1 from placebo favoring KB001-A was observed at week 16 (95% CI 1.12, 5.30, $p = 0.003$)

Table 1 continued

Name and target	Phase I trials				Phase II–III trials				
	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Key findings	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Co-Atb	Key findings
Gremubamab (MEDI3902) *PA* PcrV protein and Psl exopolysaccharide	Ali, 2018	Dose escalation 42 (56) HV	Safety and PK Incidence of AEs PK parameters	AEs were mild or moderate in severity; no sAEs were observed. Most frequent AE was infusion-related, nonanaphylactic allergic reaction One patient tested positive for ADA and found with a lower MEDI3902 serum concentration than ADA-negative subjects Linear PK across lower dosages. Nonlinear PK between the 1500 mg and 3000 mg doses	Chastre, 2022	Phase II RCT 101 (184) ICU	Prevention of PA VAP in mechanically ventilated, colonized patients Incidence of pneumonia through 21-day post-dose	No	Pneumonia incidence: 19/85 (22.4%) in study drug group vs 15/83 (18.1%) in placebo group. RRR: −23.7% [80%, CI −83.8%, 16.8%]; $p = 0.49$ Baseline ADA detected in 2/85 (2.4%) subjects in the 1500 mg group, 2/16 (12.5%) in the 500 mg group, and 3/83 (3.6%) in the placebo group. Persistent ADA similarly were present both in 1500 mg ($n = 4/85$; 4.9%) and placebo ($n = 4/83$; 5.1%) groups No differences were observed in MEDI3902 PK or safety profiles despite ADA presence

Table 1 continued

ADA anti-drug antibodies, *AE/sAE* adverse events/severe adverse events, *ATB* antibiotic, *CF* cystic fibrosis, *CI* confidence interval, *CT* clinical trial, FEV_1 forced expiratory volume in the first second, *GI* gastrointestinal, *ICU* intensive care unit, *ILs* interleukins, *ITT* intention to treat, *HAP/VAP* hospital-acquired pneumonia/ventilation-acquired pneumonia, *HR* hazard ratio, *HV* healthy volunteers, *RCT* randomized clinical trial, *MPO* myeloperoxidase, *NR* not reported, *PA Pseudomonas aeruginosa*, *PD* pharmacodynamic, *PK* pharmacokinetic, *TAEs* treatment-emergent adverse events

[a]Number of patients treated with mAb among the total number of patients included in the study

enrolling mechanically ventilated patients colonized with PA. The incidence of PA pneumonia was lower in the rivabazumab-treated groups (33% for 3 mg/kg, 31% for 10 mg/kg) compared with the placebo group (60%) within 28 days postinfusion. This corresponds to a relative risk reduction of approximately 47%, though the study was not powered for formal statistical testing [19]. However, in the randomized controlled trial (RCT) study by Jain et al., comprising 182 patients with cystic fibrosis (CF), evaluating time to antibiotic need for worsening respiratory symptoms, no significant difference between the groups was observed (HR: 1.0; 95% CI 0.7, 1.4, $p=0.995$). However, a statistically significant increase in FEV1 (+3.2%, 95% CI 1.1–5.3; $p=0.003$) was observed in the treatment group at week 16, indicating improved lung function. Notably, modest improvements in lung function and reductions in sputum inflammatory markers were observed by week 16, and a trend toward a dose-dependent reduction in sputum inflammatory markers was observed by day 28. No significant treatment-related AEs were reported, except for one SAE of elevated hepatic enzymes of unclear origin [20]. Rivabazumab, both at doses of 3 mg/kg and 10 mg/kg, was well tolerated, with no significant immunogenicity, SAEs, or AEs in two other studies [20, 21]. PK analyses in another RCT by Milla et al. showed a mean serum half-life of 11.9 days, and good lung penetration, with rivabazumab detectable in endotracheal aspirates [19, 20].

Gremubamab (MEDI3902)

Gremubamab, a bispecific IgG1 mAb targeting both the PcrV protein and the Psl exopolysaccharide of PA, was developed to prevent nosocomial PA pneumonia in high-risk patients [22]. A 2022 phase II randomized controlled trial by Chastre et al. evaluated its efficacy in mechanically ventilated intensive care unit (ICU) patients colonized with PA. Among the 85 patients receiving 1500 mg of gremubamab, the incidence of nosocomial PA pneumonia by day 21 was 22.4%, compared with 18.1% in the placebo group (80% CI–83.8%, 16.8%; $p=0.49$), indicating no significant reduction in pneumonia incidence [23]. Regarding safety, the study

Table 2 Monoclonal antibodies against *Staphylococcus* spp

Name and target	Phase I trials				Phase II–III trials				
	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Key findings	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Co-Atb	Key findings
Tosatoxumab (AR-301) Pore-forming α toxin of SA					François, 2018	Phase I/II RCT 48 (81) ICU	Safety, PK, PD, treatment of SA VAP Incidence of AEs PK parameters Clinical cure and microbiological eradication in SA VAP	Yes, not controlled	8/343 treatment-related AEs (not serious). Two withdrawals because of a sAE (one in each group). One patient developed ADA, without AEs Rate of clinical cure did not statistically differ between treatment and placebo [22 versus 14 patients (71.0 versus 87.5%); $p = 0.3892$] groups at day 28 Tendency to a shorter ventilation in study drug group compared with placebo (9.7 ± 7.87 versus 11.0 ± 7.81 day, respectively; $p = 0.4132$) Trend toward a better and faster microbiological eradication at day 28 PK profile is consistent with that of a human IgG1 mAb, with a plasma half-life of about 25 days

Table 2 continued

Name and target	Phase I trials				Phase II–III trials				
	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Key findings	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Co-Atb	Key findings
DSTA4637S (thiomab + dmDNA31) Complex: mAb and novel antibiotic directed to intracellular SA	Peck, 2019	Ascending dose RCT 20 (30) HV	Safety, PK Incidence of AEs PK parameters	No sAEs or ADA formation occurred. One moderate infusion-related reaction occurred in the 150 mg/kg DSTA4637S group. Most frequent AE: headache, nausea PK of plasma DSTA4637S conjugate and serum DSTA4637S total antibody were dose proportional					

Table 2 continued

Name and target	Phase I trials				Phase II–III trials				
	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Key findings	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Co-Atb	Key findings
Suvratoxumab (AR-320, MEDI4893) Pore-forming α toxin of SA	**Yu, 2016**	Ascending dose RCT 33 (40) HV	Safety, PK Incidence of AEs PK parameters	No sAEs occurred. Most frequent AE: rash, urticaria, GERD, vomiting Peak concentrations and concentration–time curves were dose proportional. Half-life was estimated to be 80–112 days	François, 2021	Phase II RCT 111 (213) ICU	Prevention of SA VAP, safety Incidence of SA VAP at day 30 Incidence of AEs	No	Incidence of SA VAP among SA nasal carriers at day 30: 17/96 (18%) versus placebo 26/100 (26%). RR reduction: 31.9% [90% CI −7.5 to 56.8], $p = 0.17$) Incidence of AEs and sAEs at day 30 was similar between treatment and placebo groups

Table 2 continued

Name and target	Phase I trials				Phase II–III trials				
	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Key findings	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Co-Atb	Key findings
Tefibazumab (Aurexis) ClfA	Reilley, 2005	Ascending dose CT 19 (19) HV	Safety, PK Incidence of AEs PK parameters	Treatment-emergent AEs, reported by 14/19 (73.7%) subjects. A total of 30/31 were mild, 1/31 moderate, and 6/31 possibly related to the study drug. Most frequent AE: headache The drug exhibited linear PK across the dose range of 5–20 mg/kg. The observed half-life was 22 days	Weems, 2006	Phase II RCT 30 (60) Not ICU	Treatment of SA bacteremia, Safety, PK Composite clinical end point (CCE): complications, relapse, death Incidence of AEs PK parameters	Yes, not controlled	CCE: 2/30 (0.6%) in study drug group versus 4/30 (1.3%) in placebo group Two sAEs, including one hypersensitivity reaction. Most frequent AE: hypokalemia Half-life was approximately 18 days

Table 2 continued

Name and target	Phase I trials				Phase II–III trials				
	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Key findings	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Co-Atb	Key findings
	Hethering-ton, 2006	Dose find-ing CT 8 (8) ESRD	PK in ESRD, safety PK parameters	PK param-eters were similar to those in sub-jects with normal renal function. Half-life was slightly shorter (17 versus 21 days) A total of 19 AEs in six subjects. Two sAEs, not related to the study drug					

Table 2 continued

Name and target	Phase I trials				Phase II–III trials				
	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Key findings	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Co-Atb	Key findings
Pagibaximab (BSYX-A110) LTA	Weisman, 2009	Dose finding CT 8 (8) HV	Safety, PK, PD Incidence of AEs PK parameters Opsonophagocytic activity	A total of 20 reported AEs. One sAE. None deemed related to drug Half-life was approximately 33 days Opsonophagocytic activity of serum samples on a human clinical isolate of *S. epidermidis* was dose-related	Weisman, 2011	Two dosages RCT 42 (88) Pediatric (VLBW neonates)	Prevention of sepsis, safety, PK, PD Incidence of Staphylococcical and nonstaphylococcical sepsis Incidence of AE PK parameters Opsonophagocytic activity	No	Staphylococcal sepsis: 0% in 90 mg/kg group; 13% in 60 mg/kg group, and 20% in placebo group Nonstaphylococcal sepsis: 0% in 90 mg/kg group; 10% in 60 mg/kg group, and 15% in placebo group The percentage of patients who experienced AE/sAE were similar across treatment groups. AE rate did not increase with dose. No AE was assessed as related to study drug Linear PK, a 14.5-day half-life

Table 2 continued

Name and target	Phase I trials				Phase II–III trials				
	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Key findings	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Co-Atb	Key findings
	Weisman, 2009	Phase I/II, dose escalation RCT 33 (53) Pediatric (VLBW neonates)	Safety, PK, PD Incidence of AE PK parameters Opsonophagocytic activity	52/53 patients reported at least one AE. One AE deemed related to study drug. Most frequent AEs: anemia, hyperkalemia, apnea PK appeared linear at doses ranging from 10 to 90 mg/kg Not significant difference in opsonophagocytic activity between different groups					

Table 2 continued

Name and target	Phase I trials				Phase II–III trials				
	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Key findings	Author, year	Design *N*[a] Setting	Aims Primary outcomes	Co-Atb	Key findings
ASN-100 Two components (ASN-1 and ASN-2) neutralize alpha-hemolysin and five leukocidins (including PVL)	Magyarics, 2019	Dose escalation RCT 42 (52) HV	Safety, PK, PD Incidence of AEs PK parameters Neutralizing activity	AEs were balanced between study drug and placebo groups, except for nervous system disorders. No dose-limiting toxicities or ADA formation were observed Linear serum PK. Half-life of approximately 3 weeks. Detectable penetration into the ELF Neutralizing activity was confirmed up to 58 days postdosing					

found that gremubamab was well-tolerated, with no SAEs or safety concerns. Moreover, ADA formation was assessed in this study, showing their baseline presence in a percentage of subjects across all groups, highest (2/16 patients, 12.5%) in the 500 mg group. Finally, the rate of persistent ADAs was similar between the 1500 mg and placebo groups, and their presence did not affect the PK of MEDI3902. Similarly, a phase I dose-escalation study by Ali et al. in 56 healthy adults showed good tolerability, with infusion-related reactions as the most common AEs and no SAEs. PK analysis from the phase I trial showed linear PK at lower doses, while nonlinearity was observed at 3000 mg. One participant in the highest-dose group developed ADA by day 61, which correlated with reduced serum concentrations of gremubamab between days 43 and 61 compared with ADA-negative subjects [22].

Monoclonal Antibodies Against *Staphylococcus aureus* (Table 2)

Tosatoxumab (AR-301)

Tosatoxumab is a fully human IgG1(λ) mAb that neutralizes SA alpha-toxin (Hla), which has hemolytic, cytotoxic, and dermonecrotic effects [24]. This mAb acts by binding to an N-terminal epitope of alpha-toxin and thereby preventing functional toxin pore oligomerization. By virtue of this mechanism of action, it has the potential for passive immunotherapy for *S. aureus* pneumonia and as an adjunctive therapy to standard antibiotic agents. A randomized phase I/II trial evaluated tosatoxumab safety, PK, and preliminary efficacy as an adjunct to antibiotics for severe SA pneumonia in ICU patients. Among 48 patients receiving AR-301 or placebo within 36 h of pneumonia onset, AR-301 was well tolerated, with only 2.3% (8/343) of AEs attributed to the drug and nonsevere, and only one patient developed ADAs, with no reported AEs. While underpowered for efficacy, post hoc analysis of ventilation-acquired pneumonia (VAP)s showed a numerical trend towards shorter ventilation duration and faster microbiological eradication with tosatoxumab. The trial confirmed

Table 2 continued

ADA anti-drug antibodies, *AE/sAE* adverse events/severe adverse events, *ATB* antibiotic, *BSI* bloodstream infection, *ClfA* clumping factor A, *CI* confidence interval, *CPS* capsular polysaccharide, *CT* clinical trial, *ELF* epithelial lining fluid, *ESRD* end stage renal disease, *GERD* gastro-esophageal reflux disease, *HV* healthy volunteers, *ICU* intensive care unit, *LDH* lactate dehydrogenase, *LTA* lipoteichoic acid, *NR* not reported, *PD* pharmacodynamic, *PK* pharmacokinetic, *PVL* Panton–Valentine leukocidin, *RCT* randomized clinical trial, *RR* relative risk, *SA Staphylococcus aureus*, *SdrG* Ser-Asp dipeptide repeat G, *SS* steady state, *VAP* ventilation-acquired pneumonia, *VLBW* very low-birth-weight

[a]Number of patients treated with mAb among the total number of patients included in the study

tosatoxumab's safety and indicated potential clinical benefits [25]. Results of a subsequent phase III RCT are pending [26].

DSTA4637S

DSTA4637S is an investigational antibody–antibiotic conjugate designed to target and eliminate intracellular SA, which standard antibiotics fail to address effectively. It combines an engineered human IgG1 mAb that binds to wall teichoic acid at the surface of *S. aureus* with a rifamycin-class antibiotic (dmDNA31) linked via a protease-cleavable linker, enabling targeted antibiotic delivery to infected cells. The only available study is a phase I single-ascending-dose trial in 30 healthy volunteers, which found DSTA4637S to be safe and well tolerated, with no SAE reported and no ADA formation described. PK was dose-proportional, with minimal systemic exposure to the unconjugated antibiotic, supporting a favorable safety profile [27]. A phase IB multiple-ascending-dose trial in patients with SA bacteremia receiving standard-of-care antibiotics has been registered, but results are not yet available. [28].

Suvratoxumab (AR-320, MEDI4893)

Suvratoxumab is a mAb targeting SA Hla, a key virulence factor, blocking its receptor binding and lytic activity. This antibody has been engineered to increase its half-life. The efficacy of suvratoxumab was evaluated in the SAATELLITE phase II trial, which enrolled 213 ICU patients with confirmed lower respiratory tract colonization. SA pneumonia incidence was lower in the 5000 mg group (18%) than in the placebo group (26%), with relative risk reduction of 31.9% (90% CI −7.5 to 56.8; $p=0.17$). While this did not reach statistical significance, the effect size suggests a potential protective trend in colonized ICU patients. Suvratoxumab was well tolerated, with adverse event rates comparable to placebo [29].

Lastly, a phase I study by Yu et al. demonstrated linear PK, with a terminal half-life of 80–112 days, significantly longer than typical human IgG antibodies. Serum drug levels correlated with alpha-toxin neutralization activity [30].

Further clinical trials, notably phase III trials, were suspended owing to a financial conflict between AstraZeneca and its partner Aridis Pharmaceuticals [31–33].

Tefibazumab (Aurexis)

Tefibazumab is a humanized IgG1(k) mAb with high affinity for ClfA, a surface protein expressed by SA, on a microbial surface components recognizing adhesive matrix molecules (MSCRAMM) protein that mediates the adhesion of *S. aureus* to fibrinogen. This antibody protects against ClfA-mediated destruction of host cells, preserving the human immune cells. It has undergone multiple clinical trials.

A phase II randomized, double-blind, multicenter study compared tefibazumab (20 mg/kg single infusion) with placebo in 60 patients with SA bacteraemia, alongside standard antibiotics. Although the primary focus was safety, none of the tefibazumab-treated patients experienced sepsis progression, compared with four in the placebo group; this numerical improvement of outcomes may suggest a potential benefit, despite no statistical significance being reached [34].

Tefibazumab was well tolerated, with a safety profile comparable to other mAbs. PK analysis from two phase I dose-ascending studies showed linear kinetics, including in subjects with end-stage renal disease, with a mean elimination half-life of 22 days [35, 36].

Another trial of tefibazumab in patients with CF colonized with SA was registered, but results are not available [37].

Pagibaximab (BSYX-A110)

Pagibaximab is a chimeric IgG1 mAb targeting anti-lipoteichoic acid (LTA) of SA and *S. epidermidis*. LTA plays an important role in the initiation and progression of bacterial infection, inflammation, and septic shock. In a phase II randomized, placebo-controlled trial involving 88 very low-birth-weight (VLBW) neonates, three weekly infusions of pagibaximab (60 or 90 mg/kg) were tested. No cases of

staphylococcal sepsis occurred in the 90 mg/kg group, suggesting a potential dose-dependent protective effect. Safety assessments confirmed that pagibaximab was well tolerated, with no significant differences in adverse events between treatment and placebo groups [38].

PK analysis from a phase I and a phase I/II trial indicated a favorable profile in VLBW neonates and healthy adults [39, 40].

ASN100

ASN-100 is a mAb combination comprising two fully human IgG1(k) antibodies, ASN-1 and ASN-2, which neutralize six SA cytotoxins, including Hla and Panton–Valentine leukocidin (PVL). ASN-1 neutralizes Hla and four bicomponent leukocidins: LukSF-PV (Panton–Valentine leukocidin), LukED, and two gamma-hemolysins, HlgAB and HlgCB. ASN-2 neutralizes the fifth leukocidin, LukGH (also known as LukAB).

A randomized, double-blind, placebo-controlled, phase I, single-ascending-dose trial evaluated ASN-100's safety, tolerability, and PK in 52 healthy volunteers. Participants received ASN-1, ASN-2, the combination (ASN-100), or placebo. ASN-100 was well tolerated, with mild, transient adverse events and no dose-limiting toxicities. PK was linear, with a 3-week half-life, and ASN-100 demonstrated penetration into lung epithelial lining fluid (ELF). No ADA responses were observed, and toxin-neutralizing activity in serum was sustained up to 58 days postdosing [41].

The development of the combination ASN100 was stopped due to futility in 2018 [33].

Summary of PA and SA Antimicrobial Resistance Profiles

In the study by Chastre et al., no pan-drug-resistant isolate was found, and extensively-drug-resistant isolates were balanced among groups (range 16.9–25.6%). The study arm receiving the highest dosage of the study drug (1500 mg MEDI3902) presented the highest percentage of nonMDR PA isolates, as well as the highest frequency of the combined outcome all-cause pneumonia or death (30/85 versus 22/83 in the placebo group) [23]. In the study by Lu et al., antibiograms were collected at baseline from 16 patients; seven *P. aeruginosa* isolates were resistant to carbapenems, six to ciprofloxacin, two to aminoglycosides, three to ceftazidime, and one to piperacillin/tazobactam, and in 5 out of 11 cases, PA was resistant to ticarcillin and clavulanic acid. No safety, PK, or potential efficacy conclusion was drawn according to antimicrobial resistance because of limited sample size and single-arm study design [17]. In the study by Weems et al., 30% (9/30) of patients receiving the study drug (tefibazumab) versus 50% (15/30) of patients receiving placebo had methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia, while adverse events were similar among groups; patients receiving placebo experienced a higher number of deaths and sepsis progression (4 versus 1, and 4 versus 0; respectively) [34]. In contrast, a higher number of patients in the study drug arm received cephalosporins, which the author ascribed to lower MRSA prevalence. In the 2018 study by François et al., overall MRSA prevalence was below 15% (12.5%, 6/48), resulting in two patients with MRSA per study arm; no safety or PK considerations were made according to resistance profiles. Half of the patients with MRSA (3/6) received incorrect antimicrobial therapy for the first 72 h since enrollment, potentially influencing outcomes [25]. Lastly, in the 2021 study by François et al., the authors concluded that since only 12 (6%) of 196 patients in the study were colonized by MRSA, no inferences regarding the effects of suvratoxumab in these patients were to be made [29].

Risk of Bias Assessment

We performed risk of bias assessment using the ROB2 tool for safety and clinical efficacy outcomes. While the evaluation of the former was standardized across various studies, metrics of clinical efficacy were various, and rarely more

than two studies evaluated mAb efficacy using the same metrics.

Risk of Bias Assessment for Safety Outcomes

All included studies presented safety outcomes and were either assessed with the ROB2 tool (17/18) or with the ROBINS-I V2 (1/18), as appropriate. Most RCTs were judged at low risk of bias across most of the different domains using the ROB2 tool, indicating a robust study design. Nonetheless, the overall risk of bias for safety outcomes according to the ROB2 algorithm was deemed to be "some concern of bias" because 70% (70.6%, 12/17 studies) of analyzed studies were classified at "some concern of bias" in the "selection of the reported results" domain. Otherwise, the randomization process, blinding, outcome measurement, and reporting were generally well addressed. In contrast, a limited number of trials (e.g., [40]) showed high risk of bias, mainly owing to insufficient randomization procedures and selective reporting. In addition, the only single-arm nonrandomized study evaluated with the ROBINS-I V2 tool was judged at "serious" risk of bias, revealing substantial methodological limitations, including serious bias owing to confounding and misclassification of interventions. Detailed results of the risk-of-bias assessment for the safety outcomes of included studies are shown in Supplementary Figs. 1 and 3.

Risk of Bias Assessment for Efficacy Outcomes

A total of nine studies presented efficacy outcomes and were either assessed with the ROB2 tool (8/9) or with the ROBINS-I V2 (1/9), as appropriate. All eight efficacy studies evaluated with the ROB2 tool raised "some concerns of bias," again, the "selection of the reported results" domain being the most frequently flagged as a potential source of bias, particularly because of the lack of a prespecified efficacy analysis plan. Furthermore, in the evaluation of efficacy end points, three studies [23, 25, 34] displayed an increased risk of bias originating from the randomization process, compared with the safety end points ROB2 evaluation, mostly because the isolates' resistance profile, or the clinical severity at baseline, were different among arms. Furthermore, the 2021 study by François et al. displayed a more significant bias because of missing outcome data, since its primary analysis assumption (death equals to no pneumonia) could bias results in favor of the intervention group. Lastly, the only study evaluated with ROBINS-I V2 [17] confirmed the already observed overall serious risk of bias score, but further bias was considered to characterize the "deviations from standard interventions" domain because four patients with adverse events who died during treatment were excluded from the efficacy analyses. Detailed results of the risk-of-bias assessment for the safety outcomes of included studies are shown in Supplementary Figs. 1 and 3.

Summary of clinical findings

Across the 18 included trials, mAbs were consistently well tolerated, with minimal drug-related serious adverse events. PK data were favorable, showing prolonged half-lives and consistent systemic exposure. A total of six studies (33.3%), three in both SA and PA, investigated ADA formation at baseline or after exposure to the study drugs, generally reporting no significant ADA formation, with sporadic low-titer ADAs that were not associated with clinical consequences. Several studies reported numerical trends suggestive of efficacy. Prophylaxis studies suggested potential benefits: suvratoxumab and rivabazumab demonstrated numerical reductions in pneumonia incidence—with relative risk reductions of 31.9% and 47%, respectively—while gremubamab failed to show significant differences. Notably, pagibaximab showed complete protection from staphylococcal sepsis in neonates at the highest dose. Treatment studies yielded more heterogeneous results: panobacumab demonstrated favorable safety and resolution rates in PA *pneumonia*, although in an uncontrolled setting. Rivabazumab improved FEV1 in patients with CF with chronic PA infection, but did not delay time to antibiotic requirement. Tosatoxumab showed trends towards faster microbiological eradication and reduced ventilation duration in *S. aureus* pneumonia. Tefibazumab was associated with a lower rate of sepsis progression

in patients with *S. aureus* bacteremia, although not reaching statistical significance. While these findings are not conclusive, they highlight the therapeutic potential of mAbs and warrant further clinical investigation.

DISCUSSION

We systematically reported the efficacy and safety of antibodies against the main critical pathogens that, according to the WHO, may develop resistance and pose a global threat.

This scoping review was not able to properly map safety and efficacy outcomes for MDROs, as the resistance mechanisms were scarcely described in the included studies. In the five studies that mentioned susceptibility to any antimicrobial agent or described resistance mechanisms, the proportion of patients with an MDRO infection never underwent further subgroup analysis, making specific considerations on the basis of resistance mechanisms not viable. Owing to the paucity of clinical trials specifically addressed to MDRO, we included all clinical trials involving mAbs against *Staphylococcus* spp. and PA to provide a comprehensive overview of available evidence. No clinical trials involving other WHO-priority gram-positive or gram-negative bacteria were identified through our search.

Overall, mAbs against PA and *Staphylococcus* spp. showed promising safety and PK profiles. Prophylaxis studies with suvratoxumab, rivabazumab, gremubamab, and pagibaximab suggested trends toward reduced pneumonia or sepsis incidence, although without consistent statistical significance. Treatment studies, including panobacumab, rivabazumab (in CF), tosatoxumab, and tefibazumab, showed variable clinical outcomes, with some signals of benefit in selected populations. However, these findings remain inconclusive, and no mAbs are currently used in clinical practice.

With the global spread of virulent and persistent bacteria and their resistance genes, alternative strategies for infection treatment have become increasingly necessary. The first clinically approved mAbs were developed against bacterial toxins, key virulence factors in pathogens such as *Clostridioides difficile* and *Bacillus anthracis* [42, 43]. Building on this approach, research has continued by developing antibodies targeting specific virulence or pathogenicity factors in bacteria.

Our study found evidence on mAbs mainly against PA and SA, showing a highly specific mechanism of action and extended half-life, yet variable efficacy. In fact, panobacumab, targeting PA, exhibited a favorable safety and PK profile in an uncontrolled study, but failed to demonstrate clear clinical benefits owing to heterogeneity in infection types and inconsistent antibiotic coadministration. Similarly, rivabazumab and gremubamab showed a potential effect on bacterial colonization in ventilated patients, but no statistically significant reduction in pneumonia.

Similarly, for *Staphylococcus* spp., results were heterogeneous. MAbs such as tosatoxumab and suvratoxumab showed preliminary benefits without statistically significant results. In terms of safety and tolerability, most mAbs demonstrated a favorable profile, with minimal AEs. Their prolonged half-life allowed for sustained therapeutic concentrations, reducing the need for frequent administration.

However, some studies reported immunogenic reactions, including the formation of ADAs, which could cause toxicity while reducing long-term efficacy [44].

An important limitation of our analysis, which warrants deeper consideration, is the lack of comprehensive data on ADAs across the included trials. Immunogenicity remains a critical factor in the clinical use of mAbs, as the development of ADAs can reduce drug exposure through increased clearance, alter pharmacokinetics, and potentially neutralize therapeutic effects [45]. In some cases, ADAs have been associated with loss of efficacy or increased adverse events, especially hypersensitivity reactions [46].

Despite these well-documented risks, only one in three trials in our review reported ADA data in detail. The absence of immunogenicity reporting in the remaining trials limits our ability to fully assess the clinical reliability and generalizability of the findings. This underreporting may stem from inconsistencies in

ADA testing methodologies, lack of standardized thresholds for clinical relevance, or the relatively short duration of follow-up in some studies. However, regardless of the cause, this represents a significant gap, as even low incidence rates of neutralizing ADAs can have profound effects in individual patients.

Given the potential of ADAs to compromise therapeutic efficacy, particularly in chronic or repeated administration settings, we emphasize the need for future clinical trials to rigorously monitor and report ADA formation using standardized assays. In addition, longer-term studies are needed to elucidate the immunogenic risk profile of these agents and their clinical consequences over time.

The discrepancies between in vitro efficacy and in vivo clinical outcomes may be attributed to multiple factors. First, while in vitro studies highlight the antibacterial potential of mAbs, in vivo efficacy is influenced by the complexity of host–pathogen interactions, including immune response modulation, biofilm formation, and tissue penetration [47]. Timing of administration could be another important aspect: theoretically, mAbs may be most effective in the early infection stages [8]. Despite this, many trials enrolled critically ill patients with established infections, where bacterial burden and immune dysregulation may potentially limit their efficacy. In addition, interindividual differences in PK may influence therapeutic response, indicating the potential need for dose personalization in specific patient populations. Furthermore, mAbs were often studied in combination with uncontrolled antibiotics, making it difficult to isolate their specific contribution to clinical outcomes. Study heterogeneity further complicates interpretation, with clinical trials including individuals with varying degrees of illness severity, comorbidities, and immune status, making it challenging to demonstrate a uniform therapeutic effect. In addition, pathogen diversity, including genetic variations and resistance mechanisms, may influence mAb performance, with strains differing in their susceptibility to antibody-mediated neutralization [48]. Lastly, the lack of consistent reporting on ADAs, makes it difficult to determine whether scarce efficacy might have stemmed from development of specific antidrug antibodies.

Future clinical trials should prioritize rigorous patient selection, ensuring that participants are enrolled on the basis of well-defined infection stages and confirmed pathogen identification. Stratification by immune status and comorbidities may help identify subgroups most likely to benefit from mAb therapy. Standardized diagnostic protocols, including the use of rapid, high-sensitivity tests and predictive biomarkers, have the potential to optimize patient selection and treatment monitoring. Trial designs should minimize confounding factors by incorporating standardized antibiotic regimens and adopting adaptive methodologies to identify effective dosing strategies early. Given the complexity of bacterial infections, combination strategies, such as mAb-antibiotic coadministration, multi-specific mAbs, or mAbs cocktails, could potentially be beneficial, yet warrant further research. Addressing immunogenicity concerns through humanized antibody designs and immune modulation strategies may be considered, with the goal of preventing ADA formation and preserving long-term effectiveness. In addition, population PK modeling could be explored to tailor dosing regimens to individual patient needs, aiming for improved safety and efficacy. Finally, the high production costs of mAbs remain a major barrier to widespread implementation, necessitating research into scalable and cost-effective manufacturing processes. However, advanced technologies such as artificial intelligence may represent promising tools to support the development and application of mAbs, although no direct evidence currently supports their use in this specific field.

A major strength of this review is its systematic approach, which comprehensively analyzes the available clinical trial data on mAbs against challenging bacteria. By including a broad range of studies, the review provides valuable insights into the safety, efficacy, and PK of these mAbs, highlighting both promising findings and key challenges. However, some limitations must be acknowledged. The first and most relevant limitation of all, the research strategy was initially modified owing to paucity of results; this surely diluted the relevance of our findings for

drug-resistant organisms, as originally planned, and hampered the methodological strength of this study. Hence, we were unable to conduct separate analyses or meta-analyses stratified by study phase; a narrative approach was chosen, inevitably hampering study rigor, objectivity, and the ability to draw quantitative conclusions. Furthermore, the lack of studies focusing on WHO priority pathogens other than SA and PA hampers the validity of our findings for other critical bacteria, for which, to our best knowledge, there are there no clinical trials in humans currently available. Secondly, both safety and efficacy outcomes were considered at some risk of bias. While safety outcomes generally showed low-to-moderate risk of bias, greater caution is needed when interpreting efficacy estimates owing to more widespread bias concerns, particularly regarding selective reporting, baseline imbalances, missing data, and exclusion of patients with adverse events. Thirdly, the lack of standardized end points across studies makes it difficult to assess the impact of mAbs on a specific clinical outcome. Finally, most trials assessed mAbs in combination with antibiotics, making it challenging to isolate their individual therapeutic contribution.

CONCLUSIONS

Despite the initial review focus, scarce and inconsistent data focusing specifically on safety, PK, or efficacy of mAbs administered against MDROs we retrieved.

Nonetheless, mAbs show promise as a novel therapeutic approach against critical bacteria, characterized by high specificity, long half-life, and potential to be used in passive immunotherapy, especially in immunocompromised patients. But there are several challenges that need to be addressed to improve clinical application. While these treatments generally have a favorable safety profile, their efficacy remains inconsistent. This is likely due to factors such as pathogen diversity, patient heterogeneity, and trial design limitations. To improve the impact of future trials, more rigorous trial designs and patients' selection are needed, along with enhanced diagnostic tools for quicker and more accurate pathogen identification.

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Data Availability. The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Being the corresponding author, I assure the Editorial Board of Infectious Diseases and Therapy that Marco Piscaglia, Giovanni Scaglione, Camilla Genovese, Fabio Borgonovo, Fabio Brivio, Flavia Rampichini, Renata Grifantini, Alessandra Bandera, Andrea Gori, Marta Colaneri, and Emanuele Palomba have nothing to disclose.

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4N5Y2). This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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