



Therapeutic Antibodies for the Treatment of Respiratory Tract Infections-Current Overview and Perspectives

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1 Review

2 Therapeutic Antibodies for the Treatment of Respiratory Tract 3 Infections – Current Overview and Perspectives.

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16 **Abstract:** respiratory tract infections (RTIs) are frequent and life-threatening diseases, accounting
17 for several millions of deaths worldwide. RTIs implicate microorganisms including viruses (in-
18 fluenza virus, coronavirus, respiratory syncytial virus (RSV)), bacteria (*Pseudomonas aeruginosa*,
19 *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Bacillus anthracis*) and fungi (*Pneumocystis spp.*,
20 *Aspergillus spp.* and very occasionally *Candida spp.*). The emergence of new pathogens, like the
21 coronavirus SARS-CoV-2, and the substantial increase in drug resistance have highlighted the
22 critical necessity to develop novel anti-infective molecules. In this context, antibodies (Ab) are be-
23 coming increasingly important in respiratory medicine and may fulfill the unmet medical needs of
24 RTIs. However, development of Ab for treating infectious diseases is less advanced than for cancer
25 and inflammatory diseases. Currently, only three Ab have been marketed for RTIs, namely against
26 the pulmonary anthrax and RSV infection, while several clinical and preclinical studies are in pro-
27 gress. This article proposes an overview of the advances in the use of Ab for the treatment of RTIs,
28 based on the analysis of clinical studies in this field. It describes Ab structure, function and phar-
29 macokinetics and discusses the opportunities offered by the various Ab formats, Ab engineering
30 and co-treatment strategies. Including the most recent literature, it finally highlights the strengths,
31 weaknesses and likely future trends of novel anti-RTI Ab armamentarium.

32 **Keywords:** therapeutic antibodies; respiratory tract infection; pharmacodynamics (PD); pharma-
33 cokinetics (PK), clinical development

35 1. Introduction

36 Respiratory tract infections (RTI) constitute the third leading cause of morbidity and
37 mortality worldwide, in both children and adults, accounting for approximately 4.25
38 million deaths *per year* [1, 2]. In addition to premature mortality, RTIs have a dramatic
39 impact on society with respect to disability, healthcare costs, and loss of productivity.
40 Thus, the prevention and control of RTIs constitute a major goal of public health.

41 RTI refer to a range of infections confined to the upper respiratory tract (rhinitis,
42 sinusitis, pharyngitis or tracheitis) and/or lower respiratory tract (mainly bronchitis,
43 pneumonia), implicating microorganisms including viruses, bacteria and fungi. Accord-
44 ing to the World Health Organization (WHO), pneumonia is more lethal in children than
45 combined mortality from measles, malaria and acquired immune deficiency syndrome
46 (AIDS) [3, 4].

After more than sixty years characterized by the use and misuse of broad-spectrum antibiotics, resistance to antibiotics and some antivirals has become a real threat, while the deficit of drugs with novel modes of action to implement the conventional armamentarium represents a critical concern. The attrition of existing therapeutic options and emergence of new viruses has complicated the management of RTIs, increasing pressure on healthcare systems and motivated development of new therapeutic strategies for RTI. Among these, antibodies (Ab) and antibody-based molecules, are now considered as a viable option, against emerging viral pathogens and antibiotic-resistant bacteria [5-9].

Ab present potential advantages compared to other antimicrobials. First, they provide a therapeutic option when vaccines or conventional drugs are neither available nor efficacious, due to compromised immune system or intrinsic resistance. Secondly, Ab usually target highly conserved, specific antigens and are associated with limited development of drug resistance. Finally, in immunocompetent patients, they may provide a prophylactic setting, acting as vaccine-like molecules through the promotion of long-term anti-microbial specific immune responses [10].

Despite extensive investments in Ab discovery and manufacturing, there are currently only three therapeutic Ab approved by the health authorities for fighting against RTI (Table 1) and fewer than twenty in clinical development. This highlights the complexity of anti-infective Ab development, especially in the field of infectious diseases, which needs to overcome scientific, regulatory and even commercial barriers before being accessible to patients.

Table 1. Approved therapeutic antibodies for respiratory infections.

Indication	Generic name	Sponsoring company	Target	Development stage
<i>Respiratory syncytial virus</i>	Palivizumab (synagis)	AstraZeneca	F-protein	Approved in 1998
<i>Bacillus anthracis</i>	Raxibacumab (abthrax)	GSK	PA	Approved in 2013
	Obiltoximab (anthim)	Elusys Therapeutics	PA	Approved in 2016

PA, protective antigen.

In this review, we described the pharmacodynamics (PD) and pharmacokinetic (PK) features of all the anti-infectious Ab against RTI that either have been approved by the regulatory agencies or are in clinical development for RTI, and outlined their strengths and limitations. Considering the relevance of Ab to benefit to respiratory infections due to emerging pathogens [11], we also highlighted Ab developed to fight the SARS-CoV-2 pandemic.

2. Methods

We undertook a search on ClinicalTrials.gov regarding trials for antibody-based therapeutics in respiratory infectious diseases referenced at January 1, 2021. The term used in different combinations were as follows: “therapeutic antibodies”, “monoclonal antibodies” and pathogen-specific terms (including: *Bacillus anthracis*, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, Group A *Streptococcus*, *Chlamydia pneumoniae*, *Chlamydia trachomatis*, *Chlamydia psittaci*, *Moraxella catarrhalis*, *Haemophilus influenza*, *Bordetella pertussis*, *Coxiella burnetii*, *Legionella pneumophila*, *Mycobacterium tuberculosis*, *Corynebacterium diphtheriae*, *Neisseria gonorrhoeae*, *Neisseria meningitis*, *Francisella tularensis*, *Xanthomonas pseudomallei*, *Yersinia pestis*, *Escherichia coli*, *Enterobacter*, *Proteus*, *Aspergillus* spp., *Pneumocystis jirovecii*, *Cryptococcus* spp., *Candida* spp., *Coccidioides immitis*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, *Paragonimus* spp., *Histoplasma capsulatum*, *Respiratory syncytial virus*, *Influenza A virus*, *Influenza B virus*, *Human papillomavirus*, SARS-CoV-2, COVID-19). The results were limited to on-going trials or trials involving entities, which development is still active (survey on

sponsoring company pipeline). They were confirmed on several drug databases (<https://chineseantibody.org/>, <https://www.antibodysociety.org/>, <https://adisinsight.springer.com/>, <https://www.covid-trials.org/>). Our methodology was further documented by specific searches on Pubmed.

3. Result

3.1. Therapeutic antibodies – main features

Since the development of the hybridoma technology by Köhler and Milstein, in the early 1970s [12] – who earned the Nobel Prize for this work – Ab and Ab-derived molecules have emerged as anti-infective options, even for emerging viral infections [5, 13]. Numerous technological advances have been done to improve the efficacy of Ab. From the first-generation murine Ab, innovative approaches have given rise to chimeric, humanized and fully human Ab, which can be sequenced, engineered, bio-produced at large scale [14, 15]. The present review will focus on immunoglobulin G (IgG) scaffold since most Ab approved or under investigation in RTI are full-length IgG. IgG contain an antigen-binding fragment (Fab) recognizing a targeted antigen with a high specificity and affinity hindering any side effect on symbiotic microflora. They also comprise a fragment crystallizable (Fc) region mediating downstream effectors function through its interaction with immune cells (*via* the engagement with various Fc receptors) or the complement component C1q. The Fc domain (*via* the engagement with the neonatal receptor for IgG, FcRn) is also intricately associated with a favorable PK, conferring theoretically to IgG a ≈ 21 day-long half-life ($T_{1/2}$) in biological fluids [16]. The mechanisms of action of Ab are multiple and attributable to their Fab region, their Fc region or both. They include direct-killing, neutralization, virulence inhibition, complement deposition, opsonophagocytosis, antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) [16].

The structural and functional properties of the natural human IgG subclasses - IgG1, IgG2, IgG3 and IgG4- can be used to generate therapeutic Ab [17]. Indeed, subclasses differ with regard to molecular structure, PD and PK profiles. However, most Ab on the market are from the IgG1 subclass, most likely because of IgG1 stability during manufacturing processes, greater potency of effector functions and serum bioavailability [18].

In addition to a multi-faceted PD, Ab PK is unique, involving specific mechanisms of absorption, catabolism and elimination. The fate of Ab depends on multiple parameters, thereby their PK displays a large inter-individual variability, which can be detrimental for clinical responses [19]. Understanding better the parameters governing Ab PK remains critical to enhance the likelihood of Ab response during RTI.

3.2. Therapeutic antibodies against virus diseases

3.2.1. Respiratory Syncytial Virus (RSV)

Human respiratory syncytial virus (RSV) belongs to the *Paramyxoviridae* family. It is an enveloped single stranded negative-sense RNA virus. Its lipid bilayer envelop contains three membrane proteins: the small hydrophobic protein (SH), the attachment glycoprotein (G) and the fusion protein (F) [20, 21]. It is noteworthy that approved and under evaluation (even discontinued) Ab indicated for RSV infection are all directed against F protein. Indeed, F protein has an essential role in RSV pathophysiology: the virus binds to host cell using the G protein, and thereafter uses the F protein to fuse with host cell membranes. As compared to G protein, F protein exhibits more conserved sequence among RSV strains and is more immunogenic [22] (Table 2).

Table 2. Therapeutic antibodies for viral respiratory infections.

Indication.	Generic name	Sponsoring company	Target	Development stage	NCT	Completion date	Status
<i>Respiratory syncytial virus</i>	MEDI-8897 (nirsevimab)	MedImmune	F-protein	Phase 2/3	NCT03959488, NCT03979313	2021-2023	Recruiting
	MK-1654	Merck	F-protein	Phase 2	NCT03524118	2022	Active
	VIR-2482	Vir Biotechnology	HA	Phase 2	NCT04033406	2022	Recruiting
<i>Influenza A virus</i>	CT-P27 (antibody mixture)	Celltrion	HA	Phase 2	NCT03511066	2018	Active on Celltrion web-site
	VIS-410	Visterra	HA	Phase 2	NCT03040141, NCT02989194, NCT02468115	2018	Active on Visterra web-site
<i>HPV-associated Recurrent Respiratory Papilloma</i>	Avelumab	Merck	PD-L1	Phase 2	NCT02859454	2019	Active
	Pembrolizumab	Merck	PD-1	Phase 2	NCT02632344	2020	Active, not yet recruiting

HA, hemagglutinin; PD1, programmed death 1; PDL1, programmed death-ligand 1.

RSV is responsible for infections, usually limited to the upper airways including low-febrile rhino-pharyngitis, but it can spread deeper into the respiratory tract leading to bronchiolitis or pneumonia. Sensitivity to RSV infection is person-dependent, but mostly involved critical cases at the extremes ages of life and especially in young children: during the first two years of life, a large majority of children contracts RSV and up to 40% developed a lower respiratory tract infection [23][24]. Despite the health care burden associated with the RSV, there is no curative antiviral drug (except the controversial ribavirin) or vaccine. The main treatment strategy relies in supportive care to relief nasal congestion, fever, dehydration or hypoxia.

Additionally to supportive care, palivizumab (Synagis®) was approved in 1998 for prophylaxis of respiratory disease caused by RSV in children at high risk. This humanized IgG1 Ab is the only approved drug targeting specifically the RSV, more precisely its F protein. Efficacy was demonstrated among children with bronchopulmonary dysplasia, with congenital heart disease or premature infants (Impact-RSV Trial).

Besides, two additional anti-RSV Ab are currently in clinical development. MEDI-8897 (nirsevimab) is a fully human IgG1 Ab developed by AstraZenca for the prevention of RSV infection [25]. Compared to palivizumab, MEDI-8897 is 9-fold more effective in reducing viral load in cotton rats. It presents also an extended $T_{1/2}$ (63–73 days in child) consecutive to the introduction of an YTE modification in the Fc fragment. In a Phase 1b/2a (NCT02290340), anti-drug antibodies (ADA) were detected, but were not associated with neither adverse effects nor a reduction in blood Ab concentration, for up to 151 days. Based on a Phase 3 clinical trial (NCT03979313), MEDI-8897 is expected to improve the prevention against RSV infection in late premature and healthy full-term child. MK-1654 is a fully human Ab targeting RSV F protein, developed by Merck. It also contains an YTE mutation to increase its serum $T_{1/2}$ [26]. Interim report from Phase 1 study (NCT03524118) characterized a PK model (developed for adults) able to predict PK in children and supports further development in children [27].

3.2.2. Human papillomavirus (HPV)

HPV, a well-known driver of genital tract lesions and cervical cancer, may also be responsible for recurrent respiratory papillomatosis (RRP). RRP is characterized by papilloma growing in the respiratory tract, and can lead to: voice changes, pulmonary lesions, airway compromise and fatal distal airway obstruction [28]. In 2018, Ahn *et al.* stained and scored by automated cell count 39 formalin-fixed paraffin-embedded RPP for CD4, CD8, FoxP3, and PD-1 [29]. They showed that most RRP specimens demonstrated PD-1 (Programmed cell Death-1) T-lymphocyte infiltration and PD-L1 (Programmed Death-Ligand 1) expression on both papilloma and infiltrating immune cells, suggesting that this checkpoint pathway may contribute to local immunosuppression in RRP. Two clinical trials are in progress to determine whether re-purposed immunotherapies targeting PD-L1 and PD-1 checkpoint pathway, originally developed to treat cancer patients, can be used to activate the immune system against HPV-infected cells (Table 2). Avelumab is a human IgG1 that binds to PD-L1 and blocks the interaction between PD-L1 and its receptors, PD-1 and B7.1. This leads to the suppression of the inhibitory effects of PD-L1 on cytotoxic CD8+ T cells, thus restoring anti-tumor responses of T lymphocytes. Avelumab also induces direct lysis of tumor cells by natural killer cells *via* ADCC [30]. A Phase 2 study (NCT02859454) is conducted to investigate the clinical activity and safety of avelumab in patients with RRP in a two-stage design with initial enrollment of 12 patients and expansion to 37 patients, if one or more complete

response(s) is/are observed in the initial group. The initial enrollment was achieved in 2019 [31]: all patients with laryngeal RRP experienced improvement in disease burden after treatment with avelumab, while no response was observed in patients suffering from pulmonary RRP. Some of the responders developed HPV-specific reactivity in papilloma-infiltrating T-cells that correlated with reduced viral load. Pembrolizumab, a humanized IgG4k directed against PD-1, prevents the interaction of PD-1 with its two known ligands PDL-1 and PDL-2 present on tumor cells [32]. In a Phase 2 study (NCT02632344), the investigators are looking at whether pembrolizumab may restore the natural ability of the immune system to recognize and eliminate HPV-infected cells.

3.2.3. Influenza virus

Influenza viruses are negative sense single-strand RNA viruses belonging to *Orthomyxoviridae* family. There are three types of human influenza viruses: A, B and C, defined according to the expression of nucleoprotein (NP) and matrix (M) protein. Type A and, to a lesser extent, type B are the most frequently encountered in the human population. Their envelope displays two main surface proteins called hemagglutinin (HA) and neuraminidase (NA). HA is implicated in virus entry in host cell *via* binding to sialic acid, preferentially in the upper airways. NA is involved in the release of the newly produced virus particles. Influenza A viruses are classified into subtypes based on HA (H1-16) and NA (N1-9) antigenic differences. Influenza viruses are responsible for seasonal influenza, which is typically limited to the upper airways and generally leads to mild symptoms including fever, sneezing, sore throat, coughing, headaches, myalgia and asthenia. However, influenza can eventually be severe when associated with secondary bacterial infection, culminating in devastating pneumonia, especially in children, elderly and chronic-disabled persons. Influenza causes 290 000 to 650 000 death *per* year worldwide with a mortality rate estimated to be 0.2% [33]. For preventive approaches, inactivated, live attenuated or recombinant-HA vaccines are available [34]. However, small mutations in HA and NA, referred to as antigenic drift, frequently occur during each epidemic season and lead to influenza evasion from immune responses. Consequently, vaccine composition is adjusted and renewed every year. Beside these small changes, major genetic recombination may occur, giving rise to viruses with entirely novel HA or NA responsible for pandemic flu such as influenza A/H1N1 in 2009. Thus, curative treatments are also necessary. Two main strategies have been considered: i) to limit the spread of the virus with NA inhibitor (oseltamivir, peramivir, zanamivir and laninamivir) or M2 ion-channel inhibitor (amantadine and rimantadine) ii) to block the viral replication with polymerase acidic (PA) endonuclease inhibitors (baloxavirmarboxil) [35].

However, the emergence of resistant viruses increases the need for new treatments and the interest for anti-influenza Ab. All Ab currently in clinical development target HA, considering its essential role on the virus lifecycle. It should also be noted that all Ab are directed against influenza A viruses (Table 2). VIS-410 is a fully human IgG1Ab (Visterra) binding to the stem region of HA, to neutralize the virus. VIS-410 appeared to be well tolerated up to a dose of 50 mg/kg (NCT02045472) [36]. In a Phase 2 placebo-controlled trial, VIS410 demonstrated a significant anti-influenza activity (NCT02989194, NCT02468115) [37, 38]. The results of a study comparing VIS410 in association with oseltamivir to oseltamivir alone (NCT03040141) showed that addition of VIS410 induced a decrease in mortality and faster virus clearance [39]. Celltrion has developed CT-P27, containing

two monoclonal Ab directed against influenza HA. *In vivo* and *in vitro* studies demonstrated its efficacy against several influenza A subtypes and the Phase 1 trial (KCT000161) showed positive safety results. A Phase 2 (NCT02071914) is ongoing. VIR-2482 (VIR Biotechnology) is an engineered Ab targeting a conserved region of HA. It is intended for flu prophylaxis, since it has a long T_{1/2}. A Phase 1/Phase 2 (NCT04033406) study was launched in 2019 to assess its safety, pharmacokinetics, immunogenicity and efficacy.

3.2.4. Pandemic Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

SARS-CoV-2 is a *Betacoronavirus*, like Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV), which are positive-sense, single-stranded RNA viruses. It consists of four major structural proteins: spike glycoproteins (S) forming spikes that hoop from the virus surface, membrane glycoproteins (M), envelope proteins (E), which are transmembrane and hemagglutinin-esterase dimer protein (HE), containing acetyl-esterase activity; and a 30 Kb RNA genome. Viral entry in host cells is achieved by exploiting the link with membrane-bound angiotensin converting enzyme II (ACE2) protein, which is expressed in different pulmonary cell types (type II alveolar cells, upper airways cells) and across the human body (e.g. endothelial cells, kidney or ileum epithelial cells). However, macrophages may also be infected by the SARS-CoV-2 [44]. This probably participates to the extrapulmonary complications associated with SARS-CoV-2. However, pulmonary infection caused by SARS-CoV-2 is the most life-threatening, resulting in some patients in an acute respiratory distress syndrome (ARDS), characterized by an impaired innate immunity, inadequate adaptive immune response, uncontrolled virus- and inflammation-induced tissue damage, and vascular permeability (Figure 1) [42]. Much of our understanding of SARS-CoV-2 immunity comes from the incredible amount of studies that has been done during the pandemic and comparison with SARS-CoV/MERS-CoV. Nonetheless, the pathogenesis of COVID-19 remains to be fully elucidated. Briefly, binding of S glycoprotein to ACE2 initiates SARS-CoV-2 entry into host cells. Fusion of the viral and cellular membranes mainly uses the serine protease TMPRSS2 (transmembrane serine protease 2) and endosomal cysteine proteases (cathepsin B and L). Once SARS-CoV-2 RNA is liberated in the host cell, it is translated and replicated – like a mRNA- using the host cell machinery. After packaging, the neo-virus is released extracellularly by budding, exocytosis and host cell death. SARS-CoV-2 is a cytopathic virus causing direct cell death during viral replication, and resulting in tissue damage and increased inflammatory response. SARS-CoV-2 replication has been shown throughout the respiratory tract.

The immune response to the virus infection usually starts at the cellular level, and plays a critical role in COVID-19 pathogenesis [45]. On one hand, SARS-CoV-2 will induce antiviral immune responses - both innate and adaptive immune responses -, with protective features to control viral infection. It may start in the endosomal compartment of infected host cells, through signaling of pattern-recognition receptors, such as Toll-like receptor 3, which will elicit production of inflammatory cytokines and in turn, activate immune cells. Innate immune cells, such as dendritic cells, macrophages and neutrophils can be activated by cytokines and damage-associated molecular patterns (DAMPs), and initiate adaptive immunity responses. On the other hand, SARS-CoV-2 may elicit pathogenic immune responses. After virus entry into cells, membrane ACE2 is downregulated, leading to imbalance of the renin-angiotensin pathway, thereby promoting angiotensin II-induced vascular

permeability and pneumonia with vascular injury. Moreover, activation of Type 1 Angiotensin II Receptor directly upregulates NF- κ B and ADAM17 ultimately leading to uncontrolled production of TNF- α and IL-6 [43]. During COVID-19 pathogenesis, activated alveolar macrophages and lung epithelial cells are the major producer of these mediators [41], which in turn will at a systemic level, mediate emergency myelopoiesis and locally, increase the expression of cell adhesion molecules and VEGF [42]. The resulting increase of lung vascular permeability will allow viral dissemination as well as leukocytes infiltration perpetuating local inflammation, leading to ARDS (Figure 1).

Over the past few months, many Ab have been developed to face the SARS-CoV-2 pandemic [40-43]. We can distinguish two categories of anti-COVID-19 Ab. The first category of anti-COVID-19 Ab is intended to reduce the symptoms and comprise mostly re-purposed Ab, targeting excessive inflammation. The second category includes Ab or Ab-based therapeutics directly targeting SARS-CoV2 (Table 3).

Table 3 Therapeutic antibodies for COVID-19 pandemic.

Strategy	Generic name	Sponsoring company	Target	Development stage	NCT (status)	Completion date
<i>ARDS-related target</i>	IC14	Implicit Bioscience	CD14	Phase 2	NCT04391309 (Active, not recruiting)	2021
	Itolizumab	Biocon	CD6	Phase 2	NCT04475588 (Completed)	2020
	Leronlimab	CytoDyn	CCR5	Phase 2	NCT04343651 (Active, not recruiting), NCT04347239 (Recruiting)	2021
	CPI-006	Corvus Pharmaceuticals	CD73	Phase 1	NCT04464395 (Recruiting)	2021
	Meplazumab	Jiangsu Pacific Meinuoke Bio Pharmaceutical	CD147	Phase 1	NCT04369586 (Recruiting)	2020
				Phase 1/2	NCT04275245 (Recruiting)	2020
				Phase 2/3	NCT04586153 (Not yet recruiting)	2021
	Lanadelumab	Takeda	Kallikrein	Phase 1/2	NCT04422509 (Recruiting)	2021
				Phase 1	NCT04460105 (Withdrawn)	2020
	Otilimab	GlaxoSmithKline	GM-CSF	Phase 2	NCT04376684 (Recruiting)	2020
	Lenzilumab	Humanigen	GM-CSF	Phase 2	NCT04583969 (Recruiting)	2021
				Phase 3	NCT04351152 (Recruiting), NCT04534725 (Not yet recruiting)	2020
	Gimsilumab	Kinevant Sciences Roivant Sciences	GM-CSF	Phase 2	NCT04351243 (Active, not recruiting)	2020/2021
	TJ003234	I-Mab Biopharma	GM-CSF	Phase 2/3	NCT04341116 (Recruiting)	2021
	Mavrilimumab	Kiniksa pharmaceuticals	GM-CSF-R	Phase 2	NCT04397497 (Not yet recruiting), NCT04463004 (Recruiting), NCT04399980 (Active, not recruiting), NCT04492514 (Recruiting)	2020–2021
				Phase 2/3	NCT04447469 (Recruiting)	2021
	Pamrevlumab	FibroGen	CTGF	Phase 2	NCT04432298 (Recruiting)	2020/2021
	SNDX-6352 (axatilimab)	Syndax Pharmaceuticals	CSF-1R	Phase 2	NCT04415073 (Suspended)	2020
				Phase 2	NCT04344782 (Active, Not yet recruiting), NCT04275414 (Completed)	2020
	BDB-001	Staidson Biopharmaceuticals	PD-L1	Phase 2/3	NCT04449588 (Recruiting)	2021/2022
	Nivolumab	Bristol-Myers Squibb	PD1	Phase 2	NCT04413838 (Active, Not yet recruiting)	2021
				Phase 2	NCT04343144 (Active, Not yet recruiting)	2020
				Phase 2	NCT04356508 (Not yet recruiting)	2021
	Crizanlizumab	Novartis	P-selectin	Phase 2	NCT04356508S	2020/2021
				Phase 2	NCT04435184 (Recruiting)	2020
				Phase 2	NCT03474965 (Recruiting)	2024

CSL312 (garadacimab)	CSL Behring	Factor XIIa	Phase 2	NCT04409509 (Recruting)	2020
LY3127804	Eli Lilly	Angiopoietin 2	Phase 2	NCT04342897 (Terminated)	2020
Ravulizumab	Alexion pharmaceuticals	C5	Phase 3	NCT04369469 (Recruting)	2020/2021
Secukinumab	Novartis	IL-17A	Phase 4	NCT04570397 (Not yet recruiting)	2021/2022
Canakinumab	Novartis	IL-1 β	Phase 2	NCT04390464 (Recruting)	2020
			Phase 2	NCT04403243 (Recruting)	2020
			Phase 3	NCT04365153 (Active, Not yet recruiting)	2020
				NCT04362813 (Active, not recruiting)	2020
				NCT04510493 (Recruting)	2023
				NCT04381052 (Not yet recruiting),	
				NCT04343989 (Recruting),	
				NCT04363502 (Recruting),	2020/2021
				NCT04494724 (Recruting),	
				NCT04348500 (Not yet recruiting)	
				NCT04659772 (Enrolling by invitation)	
				NCT04348500 (Active, not recruiting)	2021
Sirukumab	Janssen	IL-6	Phase 2	NCT04380961 (Recruting)	2021
			Phase 1	NCT04386239 (Active, Not yet recruiting)	2020
				NCT04357860 (Not yet recruiting),	
			Phase 2	NCT04357808 (Active, not recruiting),	2020/2023
				NCT04359901 (Recruting),	
				NCT04661527 (Recruting)	
				NCT04315298 (Completed),	
			Phase 2/3	NCT04324073 (Active, not recruiting), NCT04341870 (Suspended)	2021
			Phase 3	NCT04327388 (Completed),	2020/2021
				NCT04345289 (Recruting)	
				NCT04380519 (Completed),	2020-2021
			Phase 2/3	NCT04452474 (Not yet recruiting)	
Olokizumab	R-Pharm International	IL-6			
Tozilizumab + Sarilumab	Roche, Sanofi	IL-6	Phase 2	NCT04322773 (Terminated)	2021
Siltuximab	Janssen	IL-6	Phase 2	NCT04329650 (Recruting)	2020
Tocilizumab	Roche	IL-6R	Phase 1	NCT04560205 (Recruting)	2020

				NCT04445272 (Recruting), NCT04479358 (Recruting), NCT04412291 (Recruting), NCT04331795 (Completed), NCT04377659 (Active, not recruiting), NCT04363736 (Completed),	
			Phase 2	NCT04435717 (Recruting), NCT04377503 (Active, Not yet recruiting), NCT04339712 (Recruting), NCT04370834 (Suspended) , NCT04315480 (Active, not recruiting), NCT04331808 (Active, not recruiting), NCT04317092 (Active, Not yet recruiting) NCT04363853 (Active, Not yet recruiting)	2020-2022
			Phase 2/3	NCT04381936	2021/2031
			Phase 3	NCT04403685 (Terminated), NCT04423042 (Not yet recruiting), NCT04412772 (Recruting), NCT04345445 (Not yet recruiting), NCT04424056 (Not yet recruiting), NCT04335071 (Terminated), NCT04361032 (Not yet recruiting), NCT04320615 (Completed), NCT04372186 (Active, not recruiting), NCT04356937 (Active, not recruiting), NCT04577534 (Recruting)	2020-2022
			Phase 4	NCT04377750 (Recruting)	2020/2021
			Phase 3	NCT04397562 (Completed)	2021
Levilimab	Biocad	IL-6R			
Tocilizumab + Dexame- thasone	Roche	IL-6R	Phase 2	NCT04476979 (Recruting)	2021
Tocilizumab + Remdesivir	Roche	IL-6R	Phase 3	NCT04409262 (Recruting)	2020
Tocilizumab + Favipiravir	Roche	IL-6R	NA	NCT04310228 (Recruting)	2020
Tocilizumab + Siltuximab	Roche, Janssen	IL-6 + IL-6R	Phase 3	NCT04330638 (Active, not recruiting)	2020
Tocilizumab + Pembrolizum ab	Roche, Merck	IL-6R + PD-1	Phase 2	NCT04335305 (Recruting)	2020

	Tocilizumab + Hydroxychloroquine + Azithromycin	Roche	IL-6R	Phase 2	NCT04332094 (Recruting)	2020
	Heparin + Tocilizumab	Roche	IL-6R	Phase 3	NCT04600141 (Not yet recruiting)	2021
	BMS-986253	Bristol-Myers Squibb	IL-8	Phase 2	NCT04347226 (Recruting)	2021/2022
	Risankizumab	Jiangsu Pacific Meinuoke Bio Pharmaceutical	IL-23	Phase 2 Phase 2/3	NCT04583956 (Recruting) NCT04586153 (Not yet recruiting)	2021 2021
	MSTT1041A (astegolimab)	Genetech	IL-33	Phase 2	NCT04386616 (Recruting)	2020
	Emapalumab	Swedish Orphan Biovitrum	IFN- γ	Phase 2/3	NCT04324021 (Terminated)	2020
	IFX1 (vilobelimab)	InflaRx GmbH	C5a	Phase 2/3	NCT04333420 (Recruting)	2021
	Infliximab	MSD	TNF-alpha	Phase 2	NCT04425538 (Recruting)	2020
	Remdesivir + infliximab	MSD	TNF-alpha	Phase 3	NCT04593940 (Recruting)	2021
	Eculizumab	Alexion pharmaceuticals	C5	Phase 2	NCT04346797 (Recruting)	2020
	AK119	Akesobio	CD73	Phase 1	NCT04516564 (Recruting)	2021
	CERC-002	Cerecor	LIGHT	Phase 2	NCT04412057 (Recruting)	2020
	Glenzocimab	Acticor Biotech	Platelet glycoprotein VI	Phase 2	NCT04659109 (Not yet recruiting)	2021
	VIB7734	Vielia Bio	ILT7	Phase 1	NCT04526912 (Recruting)	2021
	NGM621	ngmbio	C3	Phase 1/2	NCT04582318 (Recruting)	2021
	EB05	Edesa Biotech	TLR4	Phase 2/3	NCT04401475 (Not yet recruiting)	2021
	Avdoralimab	Innate Pharma	C5aR	Phase 2	NCT04371367 (Recruting)	2020
Virus-related target	BR11-196	Brii biosciences	S protein	Phase 1	NCT04479631 (Active, not recruiting)	2021
	BR11-198		S protein	Phase 1	NCT04479644 (Active, not recruiting)	2021
	JS016	Shanghai Junshi Bioscience Co., Ltd.	S protein	Phase 1	NCT04441918 (Recruting)	2020
				Phase 1	NCT04411628 (Completed), NCT04537910 (Active, not recruiting)	2020
	LY-CoV555, LY3819253	Eli Lilly	S protein	Phase 2 Phase 2/3	NCT04427501 (Recruting) NCT04518410 (Recruting)	2020 2021
				Phase 3	NCT04497987 (Recruting), NCT04501978 (Active, not recruiting)	2021
				Phase 4	NCT04656691 (Not yet recruiting)	2021

REGN-COV2 (REGN10933 + REGN10987)	Regeneron Pharmaceu- ticals	S protein	Phase 1	NCT04519437 (Active, not recruiting)	2021
			Phase 1/2	NCT04425629 (Recruiting), NCT04426695 (Recruiting)	2020-2021
			Phase 2	NCT04666441 (Not yet recruiting)	2021
			Phase 3	NCT04452318 (Recruiting)	2021
SCTA01	Sinocelltech	S protein	Phase 1	NCT04483375 (Recruiting)	2021
			Phase 2/3	NCT04644185 (Not yet recruiting)	2021
STI-2020 (COVI-AMG TM)	Sorrento Therapeutics	S protein	Phase 1/2	NCT04584697 (Recruiting)	2021
COVI-GUARD (STI-1499)	Sorrento Therapeutics	S protein	Phase 1	NCT04454398 (Recruiting)	2021
TY027	Tychan Pte Ltd.	S protein	Phase 1	NCT04429529 (Active, not recruiting)	2020
			Phase 3	NCT04649515 (Not yet recruiting)	2021
BGB-DXP593	BeiGene	S protein	Phase 1	NCT04532294 (Recruiting)	2021
			Phase 2	NCT04551898 (Not yet recruiting)	2021
VIR-7831	Vir Biotechnology - GlaxoSmithKline	S protein	Phase 2/3	NCT04545060 (Recruiting)	2021
MW33	Mabwell Bioscience	S protein	Phase 1	NCT04533048 (Active, not recruiting)	2020
			Phase 2	NCT04627584 (Not yet recruiting)	2021
47D11	AbbVie	S protein	Phase 1	NCT04644120 (Not yet recruiting)	2021
AZD7442 (AZD8895 + AZD1061)	AstraZeneca	S protein	Phase 1	NCT04507256 (Active, not recruiting)	2021
			Phase 3	NCT04625725 (Recruiting), NCT04625972 (Recruiting)	2022
LY3832479	Junshi/Eli Lilly	S protein	Phase 2/3	NCT04441931 (Completed)	2020
HFB30132A	Hifibio		Phase 1	NCT04590430 (Recruiting)	2021
BI767551 DZIF-10c	Boehringer Ingelheim	S protein	Phase 1/2	NCT04631705 (Not yet recruiting)	2021
				NCT04631666 (Not yet recruiting)	
HLX71 fusion protein	Hengenix bio- tech/Henlius	S protein	Phase 1	NCT04583228 (Not yet recruiting)	2021
HLX70	Hengenix bio- tech/Henlius	S protein	Phase 1/2	NCT04561076 (Not yet recruiting)	
AMD03820	Olygo Bioservice		Phase 1/2	NCT04592549 (Recruiting)	2021
CT-P59	Celltrion	S protein	Phase 1/2	NCT04525079 (Recruiting)	2020
			Phase 2/3	NCT04602000 (Recruiting)	2021

CCR, CC chemokine receptor; CD, cluster of differentiation; CSF1R, colony stimulating factor 1 receptor; CTGF, Connective-tissue growth factor; GM-CSF, Granulocyte monocyte colony stimulating factor; GM-CSF-R, Granulocyte monocyte colony stimulating factor receptor; IFN- γ , Interferon gamma; IL, interleukin; IL-R, interleukin receptor; PD1, programmed cell death 1; S protein, spike protein; TNF, Tumor necrosis factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

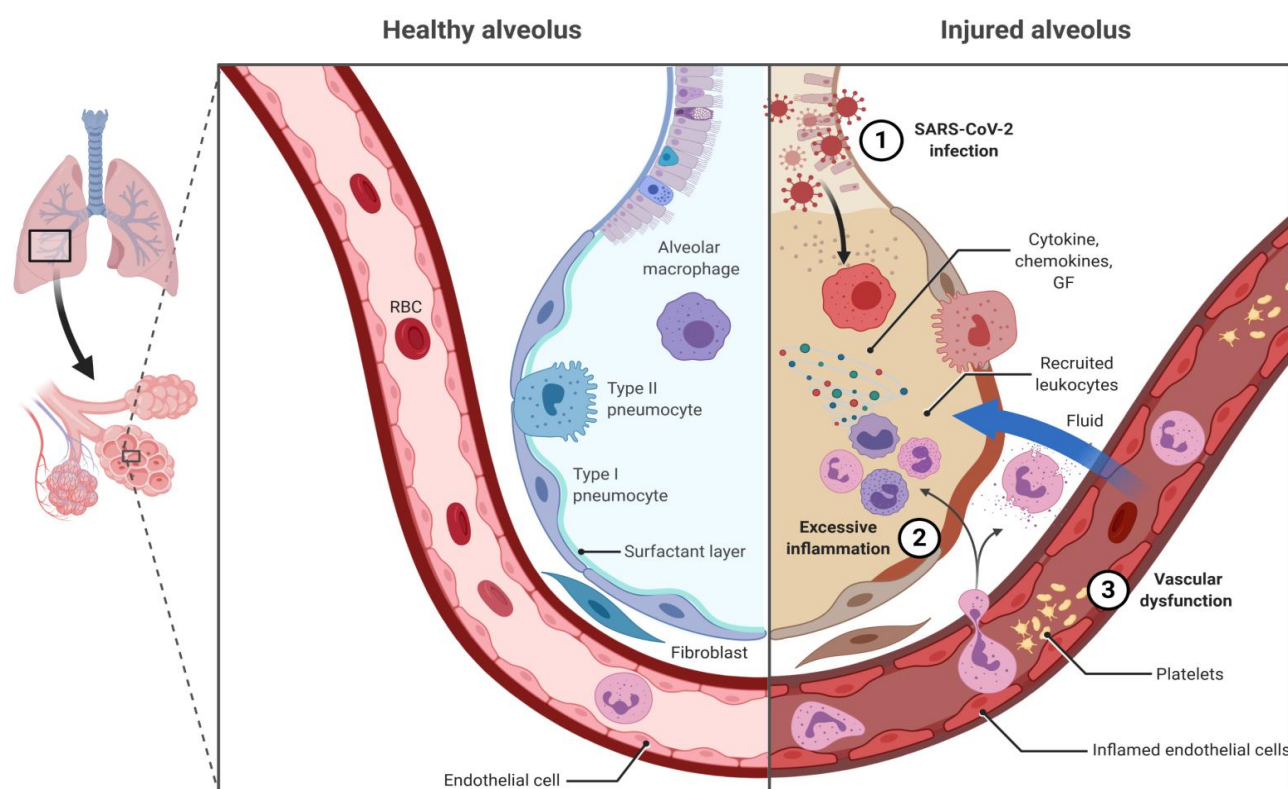


Figure 1. This figure compares the alveolar immune responses in healthy and injured lung after SARS-CoV-2 infection. 1. Coronavirus infects lung cells and encounter alveolar macrophages; 2. Alveolar macrophages identify the virus and initiate innate and acquire immune responses. Cytokines, chemokines or growth factors will attract additional immune, which will amplify and perpetuates inflammation, damaging lung alveoli and endothelium; 3. Endothelium/platelet activation and increased vascular permeability will ultimately provoke vascular dysfunction allowing virus dissemination and boost leukocytes infiltration.

Regarding the first category, several clinical trials are evaluating the potential use of antibodies targeting pro-inflammatory cytokines or their receptors. Among them, two are already approved for the treatment of COVID-19 in Russia: olokizumab and levilimab. Olokizumab, a humanized anti-IL6 IgG4 (R-Pharm International), was approved in May 2020, for patients suffering from severe COVID-19 respiratory distress. Levilimab (Biocad) is a human IgG1 that binds to soluble and membrane-bound IL-6 receptor and was also approved in Russia, in June 2020. In addition, re-purposed Ab, already approved as treatments for other diseases, are the subject of strong interest with numerous clinical trials. Sarilumab (Sanofi/Regeneron) is a human IgG1 targeting the interleukin-6 receptor. It is approved for rheumatoid arthritis in adults and currently tested in Phase 3 for hospitalized patients with COVID-19, alone or in association to tocilizumab. Tocilizumab (Hoffmann-LaRoche) is a humanized IgG1 also targeting IL-6R, marketed for several indications and is currently tested in 42 clinical trials in COVID-19 patients. First results in Europe are promising, showing an improvement of clinical outcome in patients with moderate or severe COVID-19 pneumonia [46]. Siltuximab (EUSA Pharma, BeiGene, Ltd.) is a chimeric IgG1 targeting IL-6, indicated in patients with multicentric Castleman's disease and evaluated in Phase 3 in COVID-19 (NCT04330638). Siltuximab already showed promising results in patients with COVID-19 respiratory failure, when used as compassionate treatment [47]. Emapalumab (Swedish Orphan Biovitrum) is a human IgG1 raised against interferon gamma, approved for treatment of

primary hemophagocytic lymphohistiocytosis, and evaluated in a Phase 2/3 in patients with COVID-19 (NCT04324021). Considering the involvement of the dysregulated complement cascade in severe COVID-19 complications, ravulizumab (Alexion Pharmaceuticals), a humanized IgG2/4 directed against C5, marketed for treatment of paroxysmal nocturnal hemoglobinuria, was evaluated in Phase 3 (NCT04369469).

The second category of anti-COVID-19 Ab, corresponding to more than half (including discovery and preclinical stages), targets directly SARS-CoV2. The majority are raised against S proteins to prevent binding of the virus on host cells. Among Ab-based therapeutics in development, there are polyclonal Ab, fusion proteins, single domain Ab, DARPin but the majority are monoclonal Ab. Among them, eight molecules already reached clinical trials: some are proposed as antibody cocktail (REGN-COV2, AZD7442, AMD03820), some were purified from a convalescent patient (LY3819253, CT-P59, JS016, AZD7442, HFB30132A) and most of them are fully-human monoclonal Ab. Several of those Ab have already reached phase 3 (LY-CoV555/LY3819253, REGN-COV2, SCTA01, TY027, VIR-7831, AZD7442, LY3832479, CT-P59) and two of them (LY3819253, REGN-COV2) received an Emergency Use Authorization (EUA) [48]. However, the Ab most likely to be authorized in the next months are Ab from plasma of recovering COVID-19 patients, which may benefit to hospitalized COVID-19 patients until other biotherapeutics are available. It is noteworthy that one antibody is evaluated by the inhalation route as well as the intravenous injection (BI767551 DZIF-10c, Boehringer Ingelheim). A matter of concern for the development of vaccines or therapeutic Ab against SARS-CoV2 is antibody dependent enhancement of viral entry (ADE), enhancing viral entry into cells expressing the Fc receptor for immunoglobulins. Although ADE has not been demonstrated yet for SARS-CoV-2, neutralizing Ab without effector function may be appropriate to prevent ADE.

3.3. Therapeutic Ab against bacterial diseases

With the exception of *Haemophilus influenza* type B mediating severe epiglottitis and laryngotracheitis and *Streptococcus pyogenes* causing pharyngitis and for which no antibodies are under development, bacteria are mostly associated with lower respiratory tract infections (mainly pneumonia) [49]. The most common etiologic agent of pneumonia is *Streptococcus pneumoniae*, which has a greater incidence in children and elderly [50]. Other frequent causes of bacterial pneumonia, with often multi-drug resistant phenotype, include *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Haemophilus influenza* and also bacteria grouped as atypical pneumonia (*Mycoplasma pneumoniae*, *Chlamydia spp*, *Legionella spp* or *Coxiella burnetii*) [50].

Pneumonia is characterized by an infection of the lung parenchyma. It occurs when the immune system is unable to eliminate a pathogen from the alveolar compartment [51]. The impairment of host immunity is either due to pathogen's active mechanisms (toxin or virulence factors productions) or to comorbidities (immunodeficiency, impaired mucociliary clearance, airways obstruction). The pathogen gives rise to a protracted local inflammation, which will alter lung mechanics and physiology and perpetuate damage to the lung parenchyma, accelerating systemic inflammation and worsening prognosis [52]. In the next sections, we will present and discussed the most recent advances in Ab targeting bacterial pathogens involved in RTI (Table 4).

Table 4. Therapeutic antibodies for bacterial respiratory infections.

Indication	Generic name	Sponsoring company	Target	Development stage	NCT	Completion date	Status
<i>Staphylococcus aureus</i>	MEDI4893	AstraZeneca	α -toxin	Phase 2	NCT02296320	2018	active on AZ pipeline
	AR-301	Aridis Pharmaceuticals	α -toxin	Phase 3	NCT03816956	2020	active on Aridis pipeline
<i>Bacillus anthracis</i>	Obiltoximab (anthim)	Elusys Therapeutics	PA	Phase 4	NCT03088111	2020	
<i>Pseudomonas aeruginosa</i>	AR-101 (aerumab)	Aridis Pharmaceuticals	LPS	Phase 2	NCT00851435	2009	active on Aridis pipeline
	AR-105 (aerucin)	Aridis Pharmaceuticals	Alginate	Phase2	NCT03027609	2019	active on Aridis pipeline

LPS, lipopolysaccharide; PA, protective antigen.

3.3.1. *Bacillus anthracis*

Bacillus anthracis is a spore-forming, rod-shaped, Gram-positive, facultative anaerobic bacterium, responsible for a zoonotic disease called anthrax. Humans can develop anthrax through exposure to infected animals or their products. The clinical manifestation of human anthrax varies accordingly to the mode of entry of the bacterium, with pulmonary anthrax (inhalation of spores) being the most fatal form. Apart from its animal origin, anthrax is considered to be a major bioterrorism threat. After inhalation, clinical symptoms develop usually within a week and resemble those from influenza or community-acquired pneumonia [53]. Without any treatment, pulmonary anthrax mortality ranges between 50 to 80% and coincides with the production of two main virulence factors: a capsule, which precludes the phagocytosis by host immune cells and the tripartite anthrax toxin. Anthrax toxin is composed of a protective antigen (PA), the edema factor (EF) and the lethal factor (LF) [54]. PA allows the binding, molecular re-arrangement and endocytosis of EF and LF in host cells, ultimately causing swelling and cell death. The essential role of PA in the pathophysiology of anthrax has been extensively documented and makes this protein an attractive therapeutic target [55]. Bioterrorism anthrax attacks in the USA in 2001 provoked massive investments in medical countermeasures, which resulted in the marketing of raxibacumab (ABthrax® - 2012) and obiltoxaximab (Anthim® - 2016), two Ab that neutralize PA [56, 57]. Raxibacumab is a human IgG₁, whereas obiltoxaximab is a chimeric IgG₁. A Phase 3 study in 333 human volunteers (NCT00639678) showed higher tissue concentrations of raxibacumab than those that were shown effective in animals [57]. In monkeys, obiltoxaximab allowed 100% survival if administered one to three days before anthrax exposure, and 83 to 100% survival, if given 18 to 24 hours after challenge [57]. The two Ab are indicated in adult and pediatric patients for the treatment of pulmonary anthrax in combination with standard-of-care antibacterial drugs. It is noteworthy that there is not any data related to pediatric populations, and the dose level and regimen were extrapolated from a population-based PK approach. In the clinical practice, raxibacumab is indicated for the treatment of anthrax pulmonary disease in adults at the intravenous dose of 40 mg / kg, and in children at 40 to 80 mg / kg in combination with adequate conventional antibiotics, and in prophylaxis if alternatives are not feasible. Obiltoxaximab is used in the same indications at the dosages of 16 mg / kg in adults and 16 to 32 mg / kg in children. However, pre-medication with diphenhydramine is recommended prior to obiltoxaximab administration, because it was reported to induce hypersensitivity reactions and anaphylaxis in healthy subjects [57], when it was given intravenously at 16 mg/kg. Due to the concern about adverse reactions, a Phase 4 trial has recently started (NCT03088111) to assess the clinical benefit of the use of obiltoxaximab given intravenously. Recently, very good tolerance of obiltoxaximab in randomized open-label Phase 1 trial in healthy volunteers (NCT01952444) by intramuscular route (up to 24 mg / kg) was reported [58].

3.3.2. *Staphylococcus aureus*

Staphylococcus aureus is an opportunistic Gram-positive pathogen with a significant worldwide healthcare burden. A substantial part of the human population is naturally colonized by this bacterium. Nonetheless, *S. aureus* has the ability to change from a commensal phenotype to an actual pathogen involved in various clinical manifestations, which the most serious is pneumonia, especially in hospitalized patients [59]. The recent increasing prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) strains has become a global health problem attributable to a high mortality rate [60] and complicating anti-microbial therapy. In contrast to most bacterial pathogens, *S. aureus* has the ability to secrete a large array of cytotoxins [61]. In particular, alpha-hemolysin (Hla or AT) is a key virulence factor. Once bound to its receptor (ADAM10) on host cell surface, Hla oligomerizes to form heptameric transmembrane pores, which may lyse epithelial, endothelial and immune cells. To overcome host defenses, *S. aureus* also produces five

leukocidins (SF-PV, LukED, LukGH, HlgAB and HlgCB), which target myeloid and lymphoid cells [62].

Two Ab are currently under investigation and aim at preventing or limiting *S. aureus*-related disease through the neutralization of AT. MEDI-4893 (Suvratoxumab, by AstraZeneca) has been shown to be protective in multiple animal models of pneumonia [63–65]. It is a high affinity IgG1 with an extended T_{1/2} (YTE mutated). During a Phase 2 trial, it was shown to slightly improve lung function of patients with *S. aureus* infection and was associated with low adverse events, overall encouraging AstraZeneca to continue its clinical development [66]. AR-301 (salvecin), developed by Aridis Pharmaceuticals, was designed as an adjunctive therapy to standard-of-care anti-*S. aureus* antibiotics. Even if there was not any preclinical data published, the results of a Phase 2 trial were recently presented and showed a significant reduction of time under mechanical ventilation in Ab- plus antibiotics-treated patients as compared to placebo, with good tolerance [67]. These promising results prompted a Fast Track designation by the FDA (Food and Drug Agency), an orphan-drug designation by the EMA (European Medicines Agency) and the design of a Phase 3 trial (NCT03816956), which is currently enrolling patients.

3.3.3. *Pseudomonas aeruginosa*

Pseudomonas aeruginosa (Pa) is another important nosocomial pathogen responsible for devastating acute pneumonia, in immunocompromised, ventilated patients or cystic fibrosis patients with immunologically-quiet chronic colonization. Pa versatility is related to the genetic flexibility of its large genome [68]. Many bacterial surface antigens have been considered for the development of therapeutic Ab with disappointing results. For instance, the most clinically advanced Ab is AR-101 (aerumab), a human IgM binding to lipopolysaccharide (LPS) serotype O11. LPS is an important component of *P. aeruginosa* outer membrane and has been historically used for serologic typing before genomic methods were available. In a Phase 2 trial, AR-101 given in combination with standard-of-care anti-*P. aeruginosa* antibiotics proved to be well tolerated and decrease the time to pneumonia resolution as compared to placebo [69]. Additional bacterial antigens have been considered for the development of Ab in *P. aeruginosa* strains associated with chronic colonization. Aridis Pharmaceuticals developed AR-105 (aerucin), a human IgG1, directed against *P. aeruginosa* biofilm – a complex extracellular polymeric matrix that is produced by the bacteria to increase its resistance to host immune cell and antimicrobial therapy, thereby favoring its long-term survival in the host. AR-105 targets alginate, one of the three main exopolysaccharides (with PsI, Pel) composing the biofilm [70]. It successfully completed a Phase 1 clinical trial in 16 healthy volunteers, with a good tolerance up to 20 mg/kg. FDA has granted AR-105 with fast-track designation and Aridis Pharmaceuticals initiated a Phase 2 trial in the second quarter of 2017. Results were expected to be reported in the third quarter of 2019, but there is not any information yet.

3.4. Therapeutic Ab against fungal diseases

Few therapeutic Ab have been developed against fungal diseases. Allergic bronchopulmonary aspergillosis (ABPA) mainly focuses research interests (Table 5). ABPA usually develops in patients with chronic respiratory diseases, particularly in asthmatics or in pediatric cystic fibrosis patients. Triggered by hypersensitivity immune reactions to *Aspergillus* antigens in a context of chronic *Aspergillus* tracheobronchial colonization, ABPA is an inflammatory pathology, characterized in particular by augmented titers in specific anti-*Aspergillus* IgE [71]. The main objective of ABPA therapy is to control episodes of acute inflammation and limit the progression of lung injury. Two Ab, benralizumab and dupilumab, are under clinical trials and target components of the host immune responses. Benralizumab is a humanized IgG1 that binds to the IL-5R α subunit, on eosinophils and basophils. The absence of fucose on the Fc fragment of benralizumab results in a high affinity for Fc γ RIII receptors present on the surface of

immune effector cells, such as natural killer cells. This causes apoptosis of eosinophils and basophils through ADCC. In 2019, a Japanese team reported the case of a patient with ABPA successfully treated with benralizumab [72]. A Phase 4 (NCT04108962) open-label study is now evaluating effects of benralizumab in the treatment of severe asthma in patients with allergic bronchopulmonary aspergillosis. Dupilumab is a humanized IgG4 that binds to the IL-4R α subunit thereby inhibiting IL-4 & IL-13 signaling and decreasing IgE production. A Phase 3 study (NCT04442269) is evaluating the efficacy and safety of dupilumab, in participants with ABPA, in particular the annualized rate of exacerbations.

Table 5. Monoclonal antibodies for bacterial respiratory infections.

Indication	Generic name	Sponsoring company	Target	Development		Completion	
				stage	NCT	date	Status
<i>Aspergillus fumigatus</i>	Benralizumab	MedImmune	IL-5R α	Phase 4	NCT04108962	2022	Recruiting
	Dupilumab	Regeneron Pharmaceuticals	IL-4/IL-13R	Phase 3	NCT04442269	2023	Active, not yet recruiting

IL, interleukin; IL-R: interleukin receptor.

3.5. Pharmacokinetics of anti-rti Ab

3.5.1. Administration route

Historically, Ab were mainly administered intravenously (IV). However, an increasing number of molecules have been developed for subcutaneous (SC) or intramuscular (IM) routes, the latter being used for palivizumab and obiltoximab. Absorption following SC or IM route occurs by convective transport *via* lymphatic system, leading to a time of peak blood concentration ranging from two to 10 days [56]. Distribution of Ab is limited by their hydrophilicity and high molecular mass: central and steady-state volumes of distribution are respectively 3–5 and 5–15 L. Elimination of Ab occurs *via* three main mechanisms, (i) endogenous catabolism, (ii) target-mediated elimination, and (iii) elimination mediated by ADA.

3.5.2. Endogenous (non-specific) catabolism

After cellular uptake, IgGs bind to neonatal Fc receptor (FcRn) in acidic pH conditions. FcRn ensures their protection from lysosomal degradation and recycling into the bloodstream, which explain IgG long elimination ($T_{1/2}$). Accordingly, most anti-infectious Ab - as they are IgG - have a $T_{1/2}$ of approximately 20 days. The increasing knowledge in Ab molecular biology has granted the emergence of Ab engineering with specific mutations that modulate Ab properties. In particular, mutations in the Fc portion were specifically designed to increase their affinity towards FcRn. This allowed for MEDI-4893, a dose-proportional concentrations and sustain serum exposure above target level 30 days after infusion, which may provide a longer duration of disease prevention [73]. The administration of Ab in children has been a challenge, especially anti-RSV Ab in premature infants. In general, Ab elimination seems to increase with young age [19]. The reasons remain unclear, even if a possible explanation is a decreased FcRn expression in infants. This may explain the lower $T_{1/2}$ of nirsevimab in infants than in adults [25, 74].

3.5.3. Target-mediated (specific) elimination

Ab bind to their antigen target with a high affinity; the Ab-target complex is then eliminated by immune system. Thus, Ab are drained by antigen targets. Target-mediated elimination rate is correlated to target amounts and turnover, and elimination rate of Ab-target complexes. Target-mediated elimination results in nonlinear elimination decay, which further complicates the design of optimal dosing [75].

Target-mediated elimination is often reported in dose-ranging studies, where an increase of $T_{1/2}$ with dose is observed, as and for obiltoximab [58]. At tested doses, almost all anti-infectious Ab presented linear elimination decay. However, the majority of PK studies were achieved in healthy subjects, who present null or low amount of targets and therefore no target-mediated elimination. Extrapolating PK findings in healthy subjects to define the dose and regimen in RTI patients may not be appropriate, since target-mediated elimination of Ab may be increased in infected patients, which may ultimately lead to underexposure and treatment failure.

3.5.4. Elimination mediated by anti-drug antibody

When investigated in Ab PK studies, the presence of ADA is mostly associated with increased Ab clearance, and thus decreased exposure that altogether can lead to loss of efficacy. The presence of ADA is observed in approximately 2-20% of patients, variable with antibody and underlying disease [19], primarily with palivizumab [76] and nirsevimab [25].

3.5.5. Pharmacokinetic variability, concentration-response relationship and optimal dosing

The PK of anti-infectious Ab is variable among patients and may be influenced by several factors, including age, the presence of ADA and the amount of antigen targets (viruses, bacteria or target-cells). This variability leads to a complex PK behavior for some Ab, which complicates the design of optimal dose in therapeutics. In humans, drug's PK is quantified using either non-compartmental methods or population compartmental modeling [77]. The latter one has been more and more used, because allows sound quantification of PK and concentration-effect relationship variability and the design of optimal dosing regimen. This approach is further needed in case of complex PK due to the influence of antigen burden. Up to date, PK results using this approach were reported only for palivizumab [76]. Overall, the PK of anti-infectious Ab needs further investigations; new clinical studies are needed to soundly quantify the dose-concentration-response relationship and to design optimal dosing strategies for anti-infectious Ab treatments.

4. Discussion and conclusion

Antibiotic resistance has become epidemic with projections estimating mortality from bacterial infections to be around 10 million/year in 2050, surpassing combined deaths from cancer and heart diseases [78]. In particular, ESKAPE pathogens, comprising four bacteria associated with RTI (*Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*), represent a serious healthcare issue, requiring innovative therapeutic strategies. Since the pioneer work of Von Behring and diphtheria anti-toxins serum therapy, therapeutic Ab are a promising alternative to antibiotics for infectious diseases and they have already proven successful.

Since 2018, with the exception of anti-SARS-CoV-2 Ab, the pipeline of anti-RTI Ab in clinical development has undergone a significant contraction: nine Ab have been discontinued and no novel Ab has entered in clinical evaluation [13]. This highlights that even if being a thriving focus of research, the development of anti-infectious Ab remains challenging. First, the selection of the antigenic target continues being disputed. Indeed, many Ab have been designed to bind to epitopes that are not conserved or display strain heterogeneity (e.g. lipopolysaccharides (LPS), exopolysaccharides), questioning the clinical relevance of targeting a unique pathogenic antigen. This strategy is even more arguable for viral infections, considering the rapid evolution and selection of escape mutants, especially for emerging viruses [5]. In addition, extrapolated data from animal models are fraught with conjectures in proper target selection. For example, the development of anti-*S. aureus* Ab has been hindered with the focus made on surface structure

targeting (capsule, lipoteichoic acid) and the aim of at opsonophagocytic killing, while neglecting the development of anti-toxin Ab. This was based on a misinterpretation of toxins importance in mouse model, which are nearly insensitive to leukocidins [63, 79]. In this context, refined preclinical models allowing a better understanding of the pathogenesis of lung infections and accelerated diagnostic procedures may be fundamental to improve the success of anti-RTI Ab.

Novel technologies – comprising multivalent antibodies, molecules derived from antibodies or novel formats towards antibody-drug conjugate (ADC) or antibody-antibiotic conjugate (AAC) [80] - may offer alternatives to overcome antigenic variability of pathogen and resistance to standard treatments. Antibody mixture, *e.g.* cocktails targeting different microbial pathogenic mechanisms, or Ab combined to standard-of-care antibiotics and immunomodulators may help dealing with multi-drug-resistant strains (MDR), while avoiding the appearance of cross-resistance and the disruption of the normal microflora of patients. Engineering strategies may also improve Ab's PK and/or their effector functions.

Another limitation of anti-RTI Ab development is related to their cost and their business environment. Besides the costs associated to preclinical development of any drug, Ab production is expensive, evaluated to be several ten-thousand dollars *per g* of material [81]. Business models and potential markets depend on the pathogen and may be more limited in RTI than inflammatory diseases or cancer. Moreover, development of anti-RTI Ab is hindered by uncertainties about: (i) testing preventive or therapeutic settings in patients, (ii) definition of the best-suited population for the intervention, and (iii) the choice of appropriate end-points, especially when evaluating them in acute RTI [82]. Altogether these concerns make unsure future economic returns, which may possibly explain the discontinuation of several anti-RTI Ab programs. However, it would be reasonable to put the Ab cost in view of the average expense for the treatment of patients suffering from MDR lung infections, which is estimated to be increasingly high [78, 83]. Solutions may come from innovations (i) in Ab production (plant cells based or DNA plasmid-delivered muscle cells based), which will improve yields, and (ii) in Ab delivery (considering novel intramuscular or inhalation routes), which will reduce therapeutic dosing while improving efficacy [13, 84] - both concurring to limit production costs.

Notably, the last few months has witnessed the fundamental place of Ab to fight emerging pathogens. Overall, 13 clinical trials evaluating Ab against SARS-CoV-2 are ongoing (1). Immunomodulating Ab, such as tocilizumab, already showed promising results, preventing most likely SARS-CoV-2 inflammatory-induced lung damage. This increasing global trend is kind of evidence for a strong dynamic that could place therapeutic Ab as an effective complement to the anti-RTI conventional arsenal. Along with improvements in production and engineering, this should fuel the expansion of Ab-based anti-RTI armamentarium. However, additional studies are required to decipher more clearly their PK, especially in diseased patients rather than in healthy subjects, and to investigate alternative delivery routes, like inhalation. All these issues represent substantial costs regarding preclinical and development processes, but the recent SARS-CoV-2 pandemic underscored how critical it is to relevantly promote alternative therapeutic strategies and anti-pathogen preparedness.

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