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Review

Multiple antimicrobial and immune-modulating activities of cysteamine in infectious diseases

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ABSTRACT

Infectious diseases are a major threat to global health and cause millions of deaths every year, particularly in developing countries. The emergence of multidrug resistance challenges current antimicrobial treatments, inducing uncertainty in therapeutic protocols. New compounds are therefore necessary. A drug repurposing approach could play a critical role in developing new treatments used either alone or in combination with standard therapy regimens.

Herein, we focused on cysteamine, an aminothiol endogenously synthesized by human cells during the degradation of coenzyme-A, which is a drug approved for the treatment of nephropathic cystinosis. Cysteamine influences many biological processes due to the presence of the highly reactive thiol group. This review provides an overview of cysteamine-mediated effects on different viruses, bacteria and parasites, with a particular focus on infections caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), *Mycobacterium tuberculosis*, non-tuberculous mycobacteria (NTM), and *Pseudomonas aeruginosa*.

Evidences for a potential use of cysteamine as a direct antimicrobial agent and/or a host-directed therapy, either alone or in combination with other antimicrobial drugs, are described.

1. Introduction

Infectious diseases remain a major threat to global health [1]. The spread of antimicrobial-resistant organisms and the growing number of chronic infections require new and more durable efforts to develop novel therapeutic approaches.

The repurposing of drugs used in humans for other indications has proven to be a good strategy to accelerate the identification of

Abbreviations: ACE2, the angiotensin-converting enzyme 2; BMDM, bone marrow-derived macrophages; CF, cystic fibrosis; COVID-19, Coronavirus disease-2019; CFTR, cystic fibrosis transmembrane regulator; CPE, cytopathic effects; GLS, granuloma-like structure; EMA, european medicines agency; EPS, extracellular polymeric substance; FDA, food and drug administration; HIV, human immunodeficiency virus; IAV, influenza A virus; MDM, monocyte-derived macrophages; MDR, multi-drug resistant; MLV, murine leukemia virus; NTM, non-tuberculous mycobacteria; ROS, reactive oxygen species; SARS-CoV-2, severe acute respiratory syndrome coronavirus; TG2, transglutaminase 2; TB, tuberculosis; TNF, tumor necrosis factor; VOC, variants of concern.

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compounds useful for antimicrobial therapies [2]. This field of research has experienced major progress during the coronavirus disease-2019 (COVID-19) pandemic [3,4].

A perfect drug would be a molecule that regulates immune responses to both clear the pathogen and to reduce the tissue damage elicited by the microbes and/or by the host immunity itself. Interestingly, cysteamine has both activities [5]. It is a thiol-containing drug, also known as 2-mercaptoethylamine or 2-aminoethanethiol, approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of nephropathic cystinosis, a rare inherited autosomal recessive disease. Cysteamine is an aliphatic molecule synthesized endogenously during coenzyme A metabolism as a product of pantetheine cleavage mediated by enzymes such as vanin-1 [6]. The presence of the thiol group enables cysteamine to bind and interact with the carboxyl residues of macromolecules and with the thiol or disulfide bonds of proteins [6]. Therefore, cysteamine regulates many signalling pathways that modulate the expression of genes implicated in several cellular functions such as proliferation, homeostasis, autophagy, and immune reaction. Moreover, by regulating the intracellular transport of cysteine, a precursor of glutathione synthesis, cysteamine regulates the cells' oxidative state [7].

Cysteamine is used for the treatment of cystinosis, a rare metabolic disorder caused by mutations of the cystinosin gene, a lysosomal transporter that regulates cystine efflux from lysosomes [8]. Cystinosin mutation leads to accumulation of cystine with the consequent formation of crystals, resulting in cell damage [9]. Cysteamine resolves this pathogenic process by interacting and converting cystine into both cysteine, which is released from lysosomes by a specific cysteine transport system, and cysteamine–cysteine mixed disulphide molecule, which resembles molecularly to lysine and thus is released via the specific lysine transport system [6,10].

Recently, due to its broad spectrum of actions, cysteamine has been tested in several clinical trials for different illnesses such as mitochondrial diseases, neurodegenerative and neuropsychiatric disorders, asthma, inflammatory bowel disease, melasma, non-alcoholic fatty liver disease, infantile neuronal ceroid lipofuscinosis, overweight and obesity, which have been described elsewhere [6,11–16].

Here, we will provide an overview of the potential use of cysteamine as a direct antimicrobial agent and/or a host-directed therapy in various infectious diseases (Fig. 1), with a particular focus on those caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), *Mycobacterium tuberculosis*, non-tuberculous mycobacteria (NTM), and *Pseudomonas aeruginosa*.

2. SARS-CoV-2

Since 2019 SARS-CoV-2, the etiological agent of COVID-19, has been a global concern for human health due to its high transmissibility and pathogenicity [17].

SARS-CoV-2 is a respiratory pathogen mainly transmitted via airborne droplets, aerosols or fomites [18]. COVID-19 is characterized by a wide spectrum of clinical manifestations ranging from asymptomatic to mild/moderate up to severe disease [19,20]. COVID-19 pathogenesis is a consequence of both direct virus-mediated damage to alveolar and endothelial cells, and virus-independent mechanisms that cause extensive immune dysregulation resulting in an hyper-inflammatory state (i.e. cytokine storm), and extensive lung damage [21,22].

Although WHO declared the end of COVID-19 as a public health emergency, it still represents a global threat, particularly for individuals belonging to vulnerable categories. Patients under immunosuppressive therapies, or with immune-mediated diseases, as well as elderly people, mount a lower response to vaccines [23–27] and, if infected, are prone to establishing persistent SARS-CoV-2 infections with a more severe outcome [27–36]. Moreover, persistent SARS-CoV-2 infections might favour the onset of new variants escaping host immune defence [37].

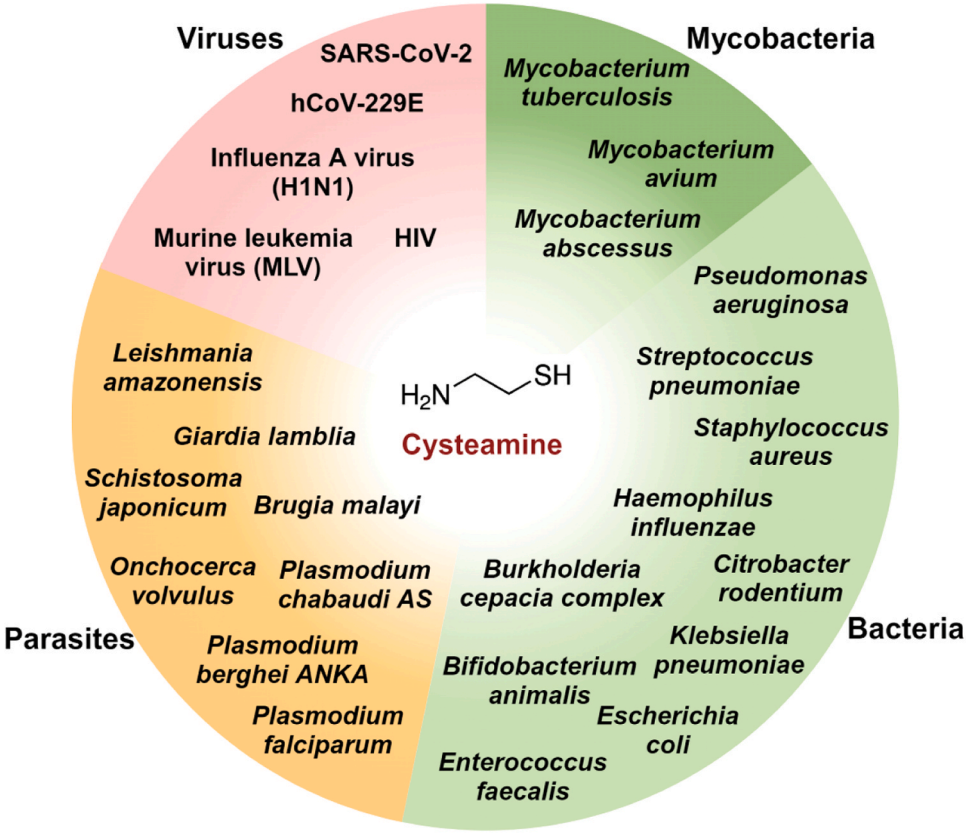

Fig. 1. Overview of microorganisms affected by cysteamine. Created with BioRender.com.

Therefore, the development of new effective adjuvant drugs is pivotal and drug repurposing can be a valid approach [3].

In this context, it has been demonstrated *in vitro* that cysteamine is effective against SARS-CoV-2 (Table 1). Cysteamine and its disulfide product of oxidation cystamine *in vitro* decrease the virus-induced cytopathic effects (CPE) in Vero E6 cells [5,38], a monkey kidney epithelial cell line [39]. This CPE-inhibitory effect was dose-dependent starting from 500 μM and 250 μM of cysteamine and cystamine, respectively, when compared to the drug vehicle [5]. Cysteamine showed a 50 % inhibitory concentration (IC50) at 180±54 μM, a concentration about 3.5-fold higher than found in the circulation of cystinosis-treated patients [40]. Furthermore, cysteamine significantly reduced the viral production of different cell lines, such as Vero E6 cells and Calu-3 cells, a human epithelial lung adenocarcinoma cell line [5], and a Vero cell line overexpressing the TMPRSS2, a transmembrane serine protease necessary for viral entry [41]. In this cell line, cysteamine was found to be active against the different SARS-CoV-2 variants of concern (VOC), with an IC50 ranging 0.7–2.0 mM, a concentration much higher than what was measured in patients' plasma under therapy [41].

Notably, cysteamine displayed a higher inhibition activity against Omicron VOC production compared to Delta and wild type [41,42]. Altogether, these results suggest that cysteamine may modify the intracellular pathways necessary for the SARS-CoV-2 life cycle.

Besides this mechanism, cysteamine directly interacts with the virus affecting its ability to interact with ACE2 (the angiotensin-converting enzyme 2), the main receptor bound by the viral spike protein to mediate cell entry [18]. Recent works demonstrated that cysteamine incubated with the spike protein alone, or with SARS-COV-2 pseudovirus or live virus, significantly reduced the number of infected cells [41,43]. This mechanism is likely due to the cleavage of cystines (Cys480-Cys488) present in the receptor binding domain (RBD) of the spike protein [43]. Moreover, cysteamine could affect other cystines present in the viral RBD, thus leading to a reduced binding capacity to ACE2. Interestingly, this mechanism is shared by different thiol-containing compounds such as Bucillamine, Tiopronin, WR-1065, N-acetylcysteine (NAC), and 2-mercaptoethane sulfonate sodium salt (Mesna) [43].

A further feature of cysteamine to counteract COVID-19 pathogenesis is its immunomodulatory action. As already observed in diseases different from COVID-19 [14–16], cysteamine decreases inflammation in both *in vitro* and *in vivo* models of SARS-CoV-2. In a whole blood platform [44], the *in vitro* treatment with cysteamine of samples from COVID-19 patients reduced the specific IFN-γ production in response to viral antigens [42]. This anti-inflammatory action was confirmed in a hamster model of COVID-19. Cysteamine treatment was associated with milder lung inflammation compared to the untreated animals, as shown by lower lung weights, and decreased levels of total proteins, neutrophils, and lymphocytes in the bronchoalveolar lavage [43]. The histopathology scores of lung tissues from cysteamine-treated animals confirmed the reduction of inflammation, alveolar haemorrhage, and tissue damage [43].

These data suggest that cysteamine may inhibit the pathogenesis of COVID-19 through three different actions: i) direct interaction with the spike protein, causing a conformational alteration that hampers its ACE2-binding capability; ii) high reactivity with intracellular thiol or disulfide-bond containing enzymes that may alter pathways necessary for SARS-CoV-2 life cycle; iii) immunomodulatory action that decreases tissue damage favouring a better disease outcome (Table 1).

Interestingly, cysteamine also inhibited the entry and replication of another coronavirus (hCoV-229E), suggesting a broader anti-coronavirus effect [38].

Overall, these *in vitro* and *in vivo* studies provide a rationale for testing cysteamine as an adjuvant therapy for COVID-19; we are currently running a trial in Italy (EudraCT number: 2022–001819–12).

Table 1
Effects of Cysteamine and/or Cystamine on viral infections.

Pathogen	Treatment	Target to:	Effect	REFs
SARS-CoV-2	Cysteamine	Virus	Decreased viral entry	[43]
	Cysteamine or Cystamine	Human and Simian cell lines	Cytopathic effect inhibition	[5,38]
			Decreased viral production (VOC)	[5,41,42]
	Cysteamine	Animal model (Hamster)	Decreased lung damage	[43]
			Reduced lung inflammation	
			Decreased total proteins, neutrophils, and lymphocytes	
	Cysteamine or Cystamine	Ex vivo (PBMC COVID-19 patients)	Downregulation of IFN-γ production	[5]
hCoV-229E	Cysteamine	Virus	Decreased viral entry	[38]
		Human cell line	Decreased viral production	[38]
HIV	Cystamine	Chronic infected cell lines	Decreased viral production by hampering the virion assembly	[78,80,81]
	Cysteamine or Cystamine	Acute infected cells	Decreased viral production by hindering pro-viral DNA production	[78,79,81]
			Inhibition of cytopathic effect and giant syncytia formation	[79,81]
	Cysteamine		Additive effects with zidovudine or didanosine	[79]
Influenza A virus (H1N1)	Cysteamine	Human cell line	Reduced viral titers and mRNA levels	[83]
Murine leukemia virus (MLV)	I-152	Animal model (Mice)	Reduced viral presence in spleen and lymph nodes	[84]
			Reduced spleen and lymph nodes weights	

Abbreviations: COVID-19, Coronavirus Disease 19; hCoV, Human Coronavirus; HIV, Human Immunodeficiency Virus; IFN, Interferon; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; VOC, Variants of Concern; PBMC: peripheral blood mononuclear cells.

3. *Mycobacterium tuberculosis* and non-tuberculous mycobacteria (NTM)

The efficacy of cysteamine against bacterial infections has been explored across various experimental models with preliminary data in a patient-based *ex vivo* study indicating a broad-spectrum activity (Table 2) [45].

Mycobacterium tuberculosis, the causative agent of tuberculosis (TB), is a slow growing bacterium that has coexisted with humans for thousands of years. TB is a worldwide disease with more than 10 million new cases and over 1 million deaths reported in 2022 [46].

M. tuberculosis mainly infects the lungs and causes immune activation, inflammation, and formation of granulomas, the hallmark of TB disease [18], which consist of monocyte-derived macrophages, foamy macrophages, epithelioid cells, and multinucleated giant cells. The persistent and dysregulated proinflammatory cytokines and chemokines production can lead to lung destruction and cavity formation [18]. Current standard therapies for TB are effective; however, nonadherence, failure, or drug resistance can occur due to the long-term treatment required [46,47]. Concomitant diseases such as human immunodeficiency virus (HIV) infection or diabetes and Tumor Necrosis Factor (TNF)α inhibitors treatment may worse clinical outcomes [48,49]. A better understanding of host-pathogen interactions and the development

Table 2
Effects of Cysteamine and/or Cystamine on bacterial infections.

Pathogen	Treatment	Target to:	Effect	REFs
Mycobacterium tuberculosis	Cysteamine or Cystamine	Human macrophages	Decreased replication of ancient and modern *Mtb* lineages Synergistic effects of Capreomycin	[50]
		Granuloma-like structure (GLS)	Decreased microbial growth Synergistic effects of amikacin	
Mycobacterium abscessus	Cysteamine	Bacterium	Decreased microbial growth Synergistic effects with amikacin or azithromycin	[45] [45,60]
	Cystamine	Human macrophages Granuloma-like structure (GLS)	Decreased microbial growth Decreased cell cytotoxicity, bacterial replication, and proinflammatory response	[60]
Mycobacterium avium	I-152	Bacterium Human macrophages	Decreased microbial growth Decreased microbial replication Regulation of cytokines production, increasing IFN-γ, IL-1β, IL-18, IL-8, IL-10 and IL-12 and decreasing TNFα	[61]
Pseudomonas aeruginosa	Cysteamine	Bacterium	Reduced cell growth, viability, and virulence factors production	[68–71]
	Cysteamine or Cystamine	Bacterium	Additive effects with ciprofloxacin, paraquat or hydrogen peroxide	[71]
	Cysteamine	Animal model (neutropenic mice)	Additive effects with ciprofloxacin	[71]
		Mono-biofilm	Reduced viability of bacteria and disrupted interfacial biofilm.	[70]
		Mono-biofilm	Additive effects with ciprofloxacin, colistin and gentamicin	[68]
		BMDM from $Cftr^{F508del/F508del}$ mice	Increased internalization and clearance of *P. aeruginosa* Decreased production of IL-1β and TNFα	[73] [73,75]
		Human macrophages of CF patients	Increased internalization and clearance of *P. aeruginosa*	[69]
Staphylococcus aureus	Cysteamine	Bacterium	Reduced cell growth and viability Synergistic effect with azithromycin	[70] [71]
		Mono-biofilm	Reduced viability of bacteria and disrupted interfacial biofilm Reduced biofilm formation of MSSA and MRSA strains	[70,86] [86]
Staphylococcus aureus and ***Streptococcus pneumoniae***	Cysteamine	Polimicrobial biofilm	Clearance of the pneumococcal population and reduced viability of S. *aureus*	[86]
Staphylococcus aureus and ***Pseudomonas aeruginosa***	Cysteamine	Polimicrobial biofilm	Reduced viability of bacteria and disrupted interfacial biofilm.	[70]
Streptococcus pneumoniae and ***Haemophilus influenzae***	Cysteamine	Polimicrobial biofilm	Reduced viability of both pathogens at low concentrations; Total clearance of both pathogens at high concentrations	[87]
Enterococcus faecalis	Cysteamine	Bacterium	Decreased microbial growth Improved the activity of metronidazole, ciprofloxacin, minocycline, and calcium hydroxide (Ca[OH]2)	[89] [89]
		Mono-biofilm	Eradication of biofilm	[88,89]
Burkholderia cepacia complex (BCC)	Cysteamine	Bacterium	Synergistic effects with tobramycin, ciprofloxacin, and trimethoprim-sulfamethoxazole	[90]
		Mono-biofilm	Antimicrobial effect only on newly biofilm formation	[90]
		Human macrophages (CF patients)	Increased bacterial killing, induced autophagy, reduced levels of TG2 reactive oxygen species, and inflammatory cytokines (IL-1β)	[69]
Escherichia coli	Cysteamine	Bacterium	Increased bacterial death in culture Additive or synergistic effect with colistin	[69] [71]
Klebsiella pneumoniae	Cysteamine	Bacterium	Additive or synergistic effect with colistin	[71]
Citrobacter rodentium	Cysteamine	Bacterium	Increased bacterial death in culture	[69]
Bifidobacterium animalis	Cysteamine	Bacterium	Increased bacterial death in culture	[69]

Abbreviations: BMDM, Bone Marrow-Derived Macrophages; CF, Cystic Fibrosis; Cftr, Cystic Fibrosis Transmembrane Regulator; IFN, Interferon; IL, Interleukin; MSSA, Methicillin-Susceptible S. aureus; MRSA, Methicillin-Resistant S. aureus. Mtb, Mycobacterium Tuberculosis; TG2, Transglutaminase 2.

of novel interventions are required.

Cysteamine or cystamine have been tested as potential antimicrobial agents showing no direct effect on *M. tuberculosis* in axenic culture [50]. However, these compounds restricted *M. tuberculosis* replication in THP-1-derived macrophages and primary macrophages [50]. Cysteamine efficacy was confirmed on several clinical isolates belonging to various phylogeographic lineages with different pathogenetic and virulence properties [50,51].

Cysteamine and cystamine showed a synergistic antimicrobial activity when administrated in combination with either capreomycin or amikacin [50].

Interestingly, similar findings were observed in the granuloma-like structure (GLS) *ex vivo* model of TB infection, in which cysteamine and cystamine had anti-*M. tuberculosis* activity when administered either alone or in combination with amikacin [50].

The antimicrobial activity of cysteamine is indirect and associated with the alteration of the autophagic flux, likely mediated by the enzyme transglutaminase 2 (TG2) [52]. The ability of cysteamine to interfere with TG2 and the STING intracellular pathway may be linked to the trigger of the antibacterial responses in macrophages [53]. These findings suggest the use of cysteamine as a potential host-directed therapy against TB by enhancing host responses and synergizing with antibiotics including the aminoglycosides, which are second-line TB drugs [50,54].

New and more effective therapeutic regimens are mostly needed against multi-drug resistant (MDR) *M. tuberculosis* strains, which are not susceptible to the most effective drugs rifampin and isoniazid. Further *in vivo* models of TB disease are needed to test the antimicrobial activity of cysteamine alone or in combination with first- or second-line drugs.

NTM are a heterogeneous group of bacteria ubiquitously present in the environment. Although generally considered of low pathogenicity to humans compared to *M. tuberculosis*, NTM are opportunistic pathogens causing disease in high-risk subjects with predisposing conditions, including patients with pre-existing lung disease and immunocompromised individuals [55].

NTM can cause a wide range of clinical diseases and the NTM-pulmonary disease is the most common. NTM are emerging as difficult-to-treat agents, with members of the *M. avium* complex and *M. abscessus* posing a significant threat particularly to vulnerable

individuals [56,57]. Current anti-NTM drug regimens are longer than those used to treat TB, have higher toxicity and lower success rate [58]. Hence, there is an urgent need to improve these regimens, and host-directed therapies are an option to overcome the lack of new antibiotics [59].

Cysteamine synergized with amikacin or azithromycin, but not with meropenem, as determined by calculating the fractional inhibitory concentration index using susceptibility assays [45]. However, cysteamine or cystamine direct activity against *M. abscessus* in axenic cultures remains uncertain because this result was obtained using non-standard microbiological assays [45], and was not confirmed when the drugs were tested in liquid and solid media or with actively growing mycobacteria [50,60].

Conversely, cysteamine had a robust anti-mycobacterial effect in infected macrophages, enhancing the response of cells against two types of *M. abscessus*, the non-cording, motile and biofilm-forming smooth (S) variant, and the cording, non-motile and non-biofilm-forming rough (R) variant [60]. Notably, cysteamine and cystamine synergized with amikacin, the most common drug used to treat *M. abscessus* infection [60]. Moreover, in the *ex vivo* model of GLS infected by *M. abscessus*, cysteamine or cystamine reduced cell cytotoxicity, bacterial replication and drastically quenched the strong proinflammatory response triggered by the most virulent rough variant of *M. abscessus* [60]. This antimicrobial effect is likely due to the ability of cysteamine to interfere with the autophagic flux through TG2 inhibition [60].

Notably, the antimicrobial activity was observed also in macrophages infected by *M. avium*. Treatment with I-152, a pro-drug that releases the two pro-glutathione molecules N-acetyl cysteine and cysteamine, inhibited intracellular mycobacteria growth [61]. Differently from what was observed for *M. abscessus*, I-152 induced a three-to six-fold increase of key chemokines and cytokines levels (i.e. IFN-γ, IL-1β, IL-18, IL-8, IL-10, and IL-12) in *M. avium*-infected macrophages. These findings were obtained using a very high (60:1) multiplicity of infection (MOI), which eventually triggered a powerful oxidative burst probably restrained by I-152 [61].

Overall, shortening current drug regimens is a major goal in the TB field as well as the development of new supportive therapies for NTM infections. Cysteamine being a safe, economical, and well-tolerated drug in humans may be a natural candidate for this purpose.

4. Pseudomonas aeruginosa

Pseudomonas aeruginosa is the most common opportunistic pathogen causing nosocomial infections, mainly in immunocompromised individuals, patients with comorbidities as well as subjects diagnosed with chronic obstructive pulmonary disease or cystic fibrosis (CF) [62]. Besides drug resistance, several mechanisms are involved in its pathogenesis including adhesion, invasion, and evasion of the immune response, making this bacterium difficult to treat [63]. The persistence of *P. aeruginosa* infection is also related to its virulence. The latter is due to the production of a wide variety of factors, including extracellular toxins and secretion of proteases (elastases LasA and LasB), which are regulated by cell-to-cell signaling systems. Most of these virulence factors are controlled by complex quorum sensing systems, which include the transcriptional regulators LasR, RhlR, and MvfR (also called PqsR) [64]. Additionally, *P. aeruginosa* exhibits a wide composition of accessory genes among strains, which modify their genomic composition allowing adaptability to different niches [65].

P. aeruginosa is the main pathogen of lung infection in CF patients, but the reason for this peculiarity has not yet been fully clarified. In CF, mutations in the CFTR (Cystic Fibrosis Transmembrane Regulator) gene lead to a dysfunctional protein. The mutated CFTR is incapable of transporting chloride ions across the cells leading to the formation of dense mucus that hampers the movement of the bronchial cilia favoring bacteriostasis [66]. In this context, *P. aeruginosa* could switch from the free-floating (planktonic) to the biofilm growth. Biofilm is a heterogeneous structure consisting of surface-associated microbial cells embedded in an extracellular polymeric substance (EPS), in which bacteria survive antibiotics better [67].

Cysteamine has antimicrobial, anti-biofilm, and mucolytic activities when used either as monotherapy or in combination with antibiotics (Table 2). Its efficacy against clinical *P. aeruginosa* isolates from CF patients has been reported both *in vitro* and in animal models. It showed a direct anti-*P. aeruginosa* activity reaching a minimum inhibitory concentration $(MIC)_{100}$ in the range of 3–10 mM [68–70]. Cysteamine and cystamine potentiate the antimicrobial activity of ciprofloxacin, both *in vitro* and *in vivo*, in the neutropenic mouse model of MDR *P. aeruginosa* infection [71]. Moreover, they increase the antimicrobial activity of paraquat and hydrogen peroxide, two reactive oxygen species (ROS)--generating chemicals, to which *P. aeruginosa* is usually resilient [71]. Cysteamine and cystamine mediate the antimicrobial activity by affecting *P. aeruginosa* metabolism (i.e. glycine as a carbon source), inducing ROS formation, and inhibiting the production of virulence factors such as phenazine pyocyanin, pyoverdine, and exopolysaccharide [71,72].

Besides the direct antimicrobial activity, cysteamine also prevented *P. aeruginosa* biofilm formation, affecting its elastic properties through the disruption of EPS matrix [70]. Notably, its action was more effective compared to rhDNAse I or alginate lyase and N-acetylcysteine, mucoactive compounds used in clinical practice [68]. This direct action was observed at a high concentration of cysteamine (about 10 mM), while a ten-fold reduced dose was not efficacious. Interestingly, this lower cysteamine concentration was effective when used in combination with tobramycin 0.01 mg/ml, which was unable to prevent biofilm formation when used as a mono-treatment [68]. The additive or synergistic antimicrobial activity of cysteamine was also observed with other conventional CF antibiotics such as ciprofloxacin, colistin, and gentamicin [68].

Cysteamine antimicrobial mechanism was described using the $Cftr^{F508del/F508del}$ mice, which produce a non-functional CFTR protein, thus representing a model of CF. The bone marrow-derived macrophages (BMDM) isolated from these mice (BMDM-CFTR-DEL) were defective in the internalization of *P. aeruginosa* and associated with an impaired microbial clearance, compared to the BMDMs isolated from wild-type mice (BMDM-CFTR-WT). Cysteamine increased both the internalization and clearance of *P. aeruginosa* in BMDM-CFTR-DEL but not in BMDM-CFTR-WT [73], as well as in peripheral blood monocyte-derived macrophages (MDM) isolated from CF patients [69].

The efficacy of cysteamine in BMDM-CFTR-DEL was due to the rescue of a functional CFTR protein. Interestingly, the rescued CFTR function led to an increase of Beclin-1 (BECN1) expression and, consequently, of the autophagic process, which is involved in *P. aeruginosa* clearance but not in the internalization process [73]. These results were confirmed in different cell lines transfected with F508del CFTR mutated gene [74]. Furthermore, the cysteamine-mediated autophagy induction was also responsible for the decreased production of the inflammatory cytokines IL-1β and TNFα released by BMDM-CFTR-DEL after 24 h of *P. aeruginosa* infection [73]. In the BMDM-CFTR-WT, cysteamine decreased the IFN-β expression through a STING-independent pathway [75].

Importantly, this beneficial effect of cysteamine in CFTR rescue and autophagy induction was observed also in combination with epigallocatechin-3-gallate (EGCG), a polyphenol with antimicrobial activity against a variety of pathogens [76], and in clinical trials conducted in CF patients carrying the F508del CFTR mutation [14,77]. These trials in humans confirmed the results generated in the mouse model, showing rescued CFTR functional protein, restoration of autophagy process, and reduction of inflammatory cytokines (i.e. TNFα and CXCL8 in the sputum). Improvement of clinical symptoms both in terms of acute bacterial exacerbations and lung function was registered, as well as the reduction of inflammatory parameters [14,77]. These results provide new insights into treatment strategies targeting *P. aeruginosa*,

supporting cysteamine as a therapeutic option in CF and other infections.

5. Other pathogens

5.1. Viruses

In addition to the pathogens described above, cysteamine has antimicrobial effects against a heterogeneous population of viruses (Table 1), bacteria (Table 2), and parasites (Table 3).

Early on, cystamine or cysteamine were shown to be promising compounds against HIV in several *in vitro* cell systems (i.e. lymphocytes, primary monocytes-derived macrophages, and monocytic and lymphocytic cell lines) [78–80].

In *de novo* infected primary lymphocytes and macrophages, both cysteamine and cystamine affected viral production, as shown by the reduced p24-antigen levels [78,79]. Moreover, they reduced the HIV-induced CPE or giant syncytia formation in $CD4^+$ T cell line (C8166), acutely infected macrophages, cord blood monocytes-derived macrophages (CBMDM), and lymphocyte cultures [79,81]. Cystamine or cysteamine inhibited HIV replication affecting the early steps of the HIV life cycle, as shown by decreased pro-viral DNA [78,79].

Moreover, cystamine reduced the HIV life cycle in chronically infected lymphocyte cell lines (H9 and ACH-2), in primary macrophages, in a macrophage cell line (U1), and in CBMDM [78,80,81], by hampering virion assembly without interfering with viral protein synthesis [78]. On the other hand, cysteamine did not show any effect on virus production in chronically infected cells [79,80]. However, it showed an additive *in vitro* antiviral effect on HIV replication in acutely infected cells when combined with zidovudine or didanosine, two reverse transcriptase inhibitors [79].

Besides the direct antiviral effect, cystamine reduced the lipopolysaccharide (LPS)-induced TNF production in primary MDM. This is particularly relevant, knowing the importance of TNF as an inducer of HIV replication [80,82]. This observation further highlights the immunomodulatory functions of cystamine/cysteamine.

Another *in vitro* antiviral effect mediated by cysteamine has been observed against influenza A virus (IAV; H1N1) in the acutely infected human alveolar epithelial carcinoma cell line A549. Cysteamine reduced both viral titers and mRNA levels of IAV in a dose-dependent manner with a maximum inhibition of 93 % at 1 mM concentration [83]. Interestingly, cysteamine did not inactivate IAV when co-incubated before infection, thus indicating that the antiviral action occurs through the modulation of host mechanisms necessary for its replication [83].

An additional antiviral action of cysteamine has been reported in mice infected by murine leukemia virus (MLV) and treated with I-152, inducing reduction of virus content, and lymph node and spleen weights [84]. This antiviral effect may be associated with the pro-glutathione action of this compound, which causes an early up-regulation of immunoproteasome subunits, thus influencing the redox-controlled immunoregulation of the host [85].

Table 3
Effects of Cysteamine and/or Cystamine on parasite infections.

Pathogen	Treatment	Target to:	Effect	REFs
Plasmodium chabaudi AS	Cysteamine or Cystamine	Animal model (Mice A/J)	Reduced blood parasitemia and mortality	[92, 93]
	Cysteamine		Synergistic effects with antimalarial drug Artemisinin	[94, 95]
		Murine erythrocytes	Reduced parasite viability	[93]
Plasmodium berghei ANKA	Cysteamine	Animal model (Mice A/J)	Synergistic effects with antimalarial drug Artemisinin	[95]
		Animal model (Mice A/J and SHIVA)	Anti-inflammatory action by reducing NLRP3 and CXCL10 production	[96]
Plasmodium falciparum	Cysteamine or Cystamine	Human erythrocytes	Inhibited parasite replication	[93]
Giardia lamblia	Cystamine	Parasite	Inhibited parasite early encystation	[97]
Onchocerca volvulus	Cystamine	Parasite	Inhibited parasite molting	[98]
Leishmania amazonensis	Cystamine	Parasite	Decreased parasite growth, development, and survival	[99]
Brugia malayi	Cystamine	Parasite	Inhibited parasite mobility, viability, and microfilariae release	[100]
Schistosoma japonicum	Cystamine	Animal model (BABL/c mice)	Reduced liver fibrosis by downregulating tTG and IL-13	[102]

Abbreviations: CXCL10, C-X-C Motif Chemokine Ligand 10; IL, Interleukin; NLRP3, Nucleotide-Binding Domain, Leucine-Rich–Containing Family, Pyrin Domain–Containing-3; tTG, Tissue Transglutaminase.

5.2. Bacteria

Cysteamine has proven to be effective also against bacteria other than mycobacteria and pseudomonas, in particular against biofilm formation (Table 2). It inhibited the growth of *Staphylococcus aureus* both in liquid culture and as mono-biofilm, reducing the biofilm elasticity by the interference with EPS matrix [68,70]. The treatment with doses of cysteamine over 2.5 mg/ml led to a 50–90 % reduction of viable *S. aureus* in the biofilm [86]. This antimicrobial effect was observed also against the biofilm formed by *S. aureus* strains either methicillin-susceptible (MSSA) or methicillin-resistant (MRSA), which were reduced by 45 % and 93 %, respectively [86].

Moreover, cysteamine exerts an antimicrobial effect against mixed biofilms generated by S. *aureus* with either *P. aeruginosa* [68,70] or *Streptococcus pneumoniae* [86]. Interestingly, within the latter mixed biofilms, cysteamine causes a complete pneumococcal population clearance [86].

This cysteamine-mediated anti-biofilm activity was observed also against the mixed biofilms of non-encapsulated *S. pneumoniae* and non-typeable *Haemophilus influenzae*. Cysteamine inhibited the 90 % viability of both pathogens when used at 0.5 and 2.5 mg/ml, while it induced almost their total clearance when used at 5 mg/ml [87].

Other biofilm formations affected by cysteamine were those generated by *Enterococcus faecalis* [88,89] and *Burkholderia cepacia complex* (BCC) [90]. Slow-growing BCC strains are often resistant to treatment and form biofilms. Interestingly, cysteamine was effective on the new BCC biofilms formation, while it did not affect those already established [90]. These data suggest the use of cysteamine as a good candidate against mono- and poly-microbial biofilms.

Additionally, cysteamine has also a direct antimicrobial activity against a wide range of bacteria, including *Burkholderia cenocepacia, Burkholderia multivorans, Escherichia coli, Citrobacter rodentium, Bifidobacterium animalis*, and *E. faecalis* during the log phase of bacterial growth (Table 2).

Importantly, cysteamine potentiates the antimicrobial activity of different antibiotics against several *Burkholderia* isolates, such as tobramycin, ciprofloxacin, and trimethoprim-sulfamethoxazole, while it had no effect on ceftazidime [90].

Cysteamine also improved the therapeutic action against *E. faecalis* of a triple combination of metronidazole, ciprofloxacin, and minocycline antibiotics, as well as calcium hydroxide (Ca[OH]2), whose bactericidal activity is due to high alkaline pH [89].

Furthermore, cysteamine has also an additive or synergistic

antimicrobial activity with colistin in resistant strains of *E. coli* (harboring the mcr-1 gene) and *Klebsiella pneumoniae* (harboring either KPC-2 or NDM-1 carbapenemase) [71]. It synergized also with the macrolide azithromycin against *S. aureus* isolates either azithromycin-resistant or azithromycin-susceptible [71].

Besides the direct antimicrobial action exerted by cysteamine, alone or in combination with antibiotics, the induction of bacterial death has been also found in MDM isolated from CF patients and infected with *B. cenocepacia* and *B. multivorans*. In these cells, cysteamine reduces the levels of TG2 protein resulting in autophagy induction, and decreases reactive oxygen species (ROS) and inflammatory cytokines [69]. Interestingly, upon cysteamine treatment *B. cenocepacia* and *B. multivorans* colocalised with LC3, a central protein in autophagy, thus implying that the cysteamine-mediated intracellular bacteria killing could be due to the induction of the autophagic process [69].

5.3. Parasites

One of the most relevant indications of cysteamine as useful drug also for parasitic diseases has been obtained in infections with five protozoan species belonging to the genus *Plasmodium* that cause malaria, with *P. falciparum* being the most virulent [91].

Cysteamine improved the clinical conditions of mice susceptible to *P. chabaudi AS* infection, an animal model of malaria [92]. These mice have mutations causing the non-expression of Vanin genes, which code for the enzyme pantetheinase involved in the production of cysteamine [6]. The treatment of these mice with cystamine or cysteamine led to reduced blood parasitemia and animal mortality [92,93].

Notably, as described above for bacteria, cysteamine potentiates the action of the antimalarial drug artemisinin by delaying the appearance of blood parasitemia, reducing parasite replication, and improving survival of mice with a lethal infection of *P. chabaudi AS* [94,95].

This combined therapy was efficacious also in a cerebral malaria mouse model infected with *P. berghei ANKA* [95]. In these mice, cysteamine had an anti-inflammatory action, reducing the production of NLRP3 (nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3) inflammasome, and the chemokine CXCL10 [96].

Importantly, the effect of cysteamine is specific because it was not observed in mice treated with dimercaptosuccinic acid, a cysteamine-related thiol, or the pantethine precursor of cysteamine [93]. Moreover, this inhibitory effect seems to be *plasmodium*-specific, as cysteamine did not protect mice from infection against another parasite as *Trypanosoma cruzi* or against the fungal pathogen *Candida albicans* [93].

In addition to these *in vivo* effects, cysteamine had also a direct anti-*Plasmodium* action. The viability of *P. chabaudi* was decreased *in vitro*, as found in treated parasitized red blood cells when reinoculated in susceptible mice [93].

Moreover, cysteamine and cystamine inhibited the *P. falciparum* replication capacity in red blood cells infected *in vitro* [93].

Since the anti-parasitic effects are detectable *in vitro* and *ex vivo* settings, thus in the absence of the host immune response, it is likely that the cysteamine has a direct anti-parasitic effect.

Overall, although the mechanisms of the antimalarial effects mediated by cysteamine are not fully understood, these results indicate the potential use of cysteamine as an adjuvant in combination with primary antimalarial therapy.

Since many parasites express proteins with a TGase activity, which is fundamental for their life cycle, cystamine has been used as a TGase inhibitor for the treatment of several parasitoses that affect different organs such as intestine (*Giardia lamblia*), skin (*Leishmania amazonensis, Onchocerca volvulus*), cornea (*Onchocerca volvulus*), liver (*Schistosoma japonicum*), and lymphatic vessels (*Brugia malayi*) (Table 3).

Cystamine was successfully used against the protein disulfide isomerases (PDI) activity of *Giardia lamblia* by inhibiting the early encystation of the parasite grown in liquid culture, thus blocking the step from trophozoites to cysts [97].

Moreover, cystamine affected also another important process of parasite maturation. Its treatment inhibited the molting of *Onchocerca volvulus*, due to an incomplete separation between the cuticle of larvae stage L3 and the L4 epicuticle [98].

In *Leishmania amazonensis* cystamine inhibited a Ca2+-independent TGase, active in both promastigotes and amastigotes, which is necessary for parasite growth, development, and survival in culture [99].

In *Brugia malayi*, cystamine inhibited the mobility and viability of the adult worm and microfilariae in culture. Moreover, it blocked the release of microfilariae by female worms, either reversibly or irreversibly, when used at low or high concentrations respectively [100].

Notably, cystamine treatment was effective also *in vivo*, in a mouse model of *Schistosoma japonicum* infection, which recapitulates the schistosomiasis hallmarks such as progressive liver fibrosis, portal hypertension, hepatosplenomegaly, and liver cirrhosis [101].

Mice infected percutaneously through the abdomen with *S. japonicum* cercariae ameliorated liver fibrosis when treated with cysteamine 3 days after infection, showing downregulation of tissue TG and, importantly, of IL-13, which is highly upregulated in untreated mice [102].

Overall, these data indicate that cysteamine could also have an important impact in several parasitic diseases (Table 3).

6. Drug formulations and pharmacokinetic characteristics

Cysteamine is approved as a therapy for preventing/reducing nephropathic cystinosis. It has side effects such as bitter taste, gastrointestinal symptoms (i.e. vomiting and diarrhea), and persistent and unpleasant sulfurous body and breath odour (i.e. halitosis). Its pharmacokinetic profile (peak at 2 hours post-assumption with a rapid decline) generates limitations on the daily and chronic use of the drug. Therefore, new formulations have been developed.

The drug currently used in clinical practice is Cystagon®, a cysteamine bitartrate formulation that allows an immediate release of the drug. The short half-life of Cystagon® (4.8±1.8 hours) requires a strict 6-hour administration schedule [103]. Moreover, Cystagon® retains several side effects.

An alternative formulation is Procysbi®, an enteric-coated cysteamine bitartrate formulation, which gradually releases the drug, thus requiring a dosing schedule every 12 hours. Moreover, it bypasses stomach absorption and limits gastrointestinal side effects [103].

A more recent formulation, still unapproved by FDA or EMA, is the prodrug TTI-0102®, an asymmetric disulfide compound containing vitamin B5 linked to two cysteamine molecules (i.e. pantothenic acid), which are actively available upon a metabolic process. In an Australian phase 1 clinical trial, TTI-0102® showed a cysteamine minimal concentration available for 24 hours, thus allowing a once-a-day administration schedule. Moreover, TTI-0102® does not reach a high peak concentration, therefore limiting the side effects [104].

New formulations that will improve the circulation bioactivity and/or topic efficacy of cysteamine are highly desirable. In particular, the nasal spray formulation could represent a valid option to treat respiratory infections such as COVID-19, TB, and NTM, possibly limiting or avoiding the known side effects of cysteamine treatment.

7. Conclusions

The presence of a thiol group makes cysteamine a highly reactive compound that influences a broad spectrum of diseases including infectious diseases (Fig. 1), through a direct action against the pathogen and/or indirectly by altering cellular functions needed for the microbe's life cycle (Fig. 2). Moreover, cysteamine has an immunomodulatory effect and synergistic action with antimicrobial drugs, which are fundamental features to improve the clinical outcome. The evidence here reported supports cysteamine as a repurposing drug for the

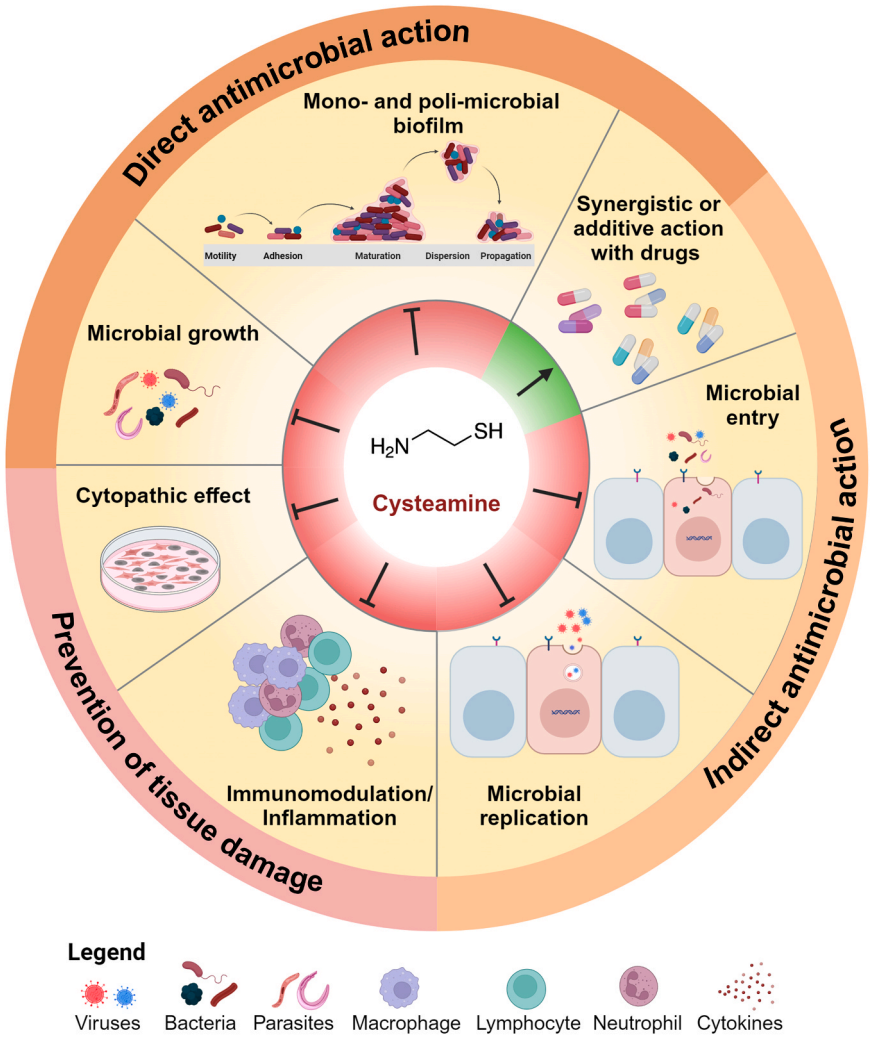

Fig. 2. Schematic representation of the different effects mediated by cysteamine on microorganisms or host cells. Created with BioRender.com.

treatment of many infectious diseases, either alone or in combination with other drugs.

Ethical approval

Not required.

Data statement

Not applicable

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CRediT authorship contribution statement

Valeria Rachela Villella: Writing – original draft, Data curation. **Valeria Raia:** Writing – original draft, Data curation. **Emanuele Nicastri:** Writing – review & editing. **Mauro Piacentini:** Writing – review & editing. **Delia Goletti:** Writing – original draft, Conceptualization. **Tonino Alonzi:** Writing – original draft, Data curation. **Alessandra Aiello:** Writing – original draft, Data curation. **Michela Sali:** Writing – original draft, Data curation. **Giovanni Delogu:** Writing – original draft, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.The authors declare no competing interests.

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