Defining "cure" for the asthmas

Current asthma treatments focus on controlling symptoms and preventing exacerbations, often requiring people to use high dose inhaled and oral corticosteroids, which can have serious and irreversible side effects. Recently, remission as a goal has received some attention,[1-3] but a cure for asthma is yet to be found, despite intensive research. Finding one remains a formidable challenge largely because asthma is not a single disease but a heterogeneous collection of distinct clinical presentations (phenotypes), each related to different pathophysiological, cellular, and molecular factors (endotypes). We often now refer to these forms as "the asthmas" and consider that multiple distinct cures may be more realistic than a single therapeutic solution.

The recent widespread adoption of high-throughput technologies has given researchers an unprecedented ability to characterise and map the molecules and pathways involved in the different asthma variants. However, in the absence of a collaborative research initiative with a unified vision for discovering cures for the asthmas, siloed research activity is unlikely to be any more effective than the paths already taken. The CURE Asthma initiative will interlace and coordinate the activities of leading Australian asthma research nodes to identify the disease mechanisms that cause the different forms of asthma, with the ultimate goal of developing curative interventions.

First, we must build on our current knowledge to define what cures for the asthmas might look like, and recognise that patients and their families, clinicians, and other interested parties may have differing views on what constitutes a cure.[4] This will establish the framework for coordinated research. Moreover, we must remain open to revising these definitions as new knowledge emerges.

Understanding remission in asthma with respect to defining "cure"

To define "cure", we must first understand remission in asthma. In chronic inflammatory conditions such as asthma, some people enter prolonged asymptomatic states, irrespective of ongoing treatment or whether the underlying pathology has resolved. This state is termed "clinical asthma remission".[1] Studying clinical remission (on or off treatment) is a valuable opportunity for uncovering mechanisms that could be targeted to achieve remission for all people with asthma.

Spontaneous remission is the natural and unexpected reduction or disappearance of disease activity. Epidemiological studies have found that 6–52% of children and 2–17% of adults with asthma experience spontaneous remission.[1] It is important to note that ongoing but silent disease activity is usual during asthma remission and may determine the future risk of relapse. Remission is also possible after complete removal of an asthma inducer; as many as 48% of people with occupational asthma, for example, experience remission within five years of removal from the implicated exposure.[5]

Treatment-induced clinical remission in asthma is a relatively new concept, and Australian clinicians and researchers are playing leading roles in the development of a global consensus for defining it.[1,6,7] A 2024 systematic review of 25 studies reported that about one-third of people with severe asthma treated with various biologic therapies experienced clinical remision.[3] Treatment-induced remission was also reported for as many as half of those with moderate to severe asthma who received long term, low dose azithromycin therapy,[7] and in about one-third of people using dual or triple single inhaler therapy.[8] Although these studies used a range of remission definitions (eg, different exacerbation and symptom criteria; diverse biomarkers and biomarker thresholds), well controlled symptoms and the sustained absence of both exacerbations and oral corticosteroid use were integral components of remission in all studies. Other criteria have been proposed, including optimisation or stabilisation of lung function and the underlying pathology, and agreement between patient and health care provider regarding remission.[1,2,9] Recently, the American College of Allergy, Asthma and Immunology, the American Academy of Allergy, Asthma, and Immunology, and an American Thoracic Society expert panel proposed a six-component definition of remission, which also included using reliever medication no more than once a month, only low to medium dose inhaled corticosteroid use, and no missed work or school over twelve months because of asthma, in addition to the symptoms, exacerbations, and lung function criteria discussed above.[10]

How is CURE distinct from remission?

Remission is not the same as cure, but it could be one pathway to cure:[11] initially achieving remission with treatment, then sustaining remission without treatment, and ultimately reaching a cured state. This process could take several years. We have as yet only achieved the first step — remission on treatment — in a subset of people with asthma. Remission can be achieved either while on or off treatment, whereas cure requires sustained disease inactivity while off treatment. Defining cure is complex, and clinicians, patients, policymakers, and pharmaceutical companies may use the term differently. Cure, in the empirical sense, may refer to the absence of disease activity that can be sustained for prolonged periods in the absence of treatment (ie, an irreversible pause in disease activity).

Some may argue that, in addition to the above criteria, a cure for asthma also requires reversal of the damaged pathological state of the airways to an age-matched, healthy normal state. However, this is not the case in oncology. The Siracusa charter defines cure in cancer as the "complete clinical remission of a cancer, regardless of the presence or absence

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of late sequelae of treatments."[12] In other words, surgical procedures or chemotherapy may leave scarring or damage, but cure (of the cancer) is still obtained. Further, epidemiologists consider statistical cure is achieved in oncology when the mortality rate returns to the baseline rate of the age-matched general population.[4] Although this definition may not be directly applicable to asthma, the underlying principles could be informative. For instance, the presence of disease or treatment sequelae may not necessarily preclude the attainment of a cured state, and it is the prolonged absence of disease activity and people living normal lives unaffected by their disease that becomes the objective. The person with asthma may envision cure as a return to the same quality of life as other people; that is, asthma no longer affects their daily life. In some cases, people may not even be aware of disease sequelae; they may also feel that the likelihood of their disease returning is sufficiently low to consider themselves effectively cured.[4] In practical terms, some of the airway pathology caused by asthma (such as airway remodelling) and iatrogenic side effects of treatment (such as osteoporosis caused by oral corticosteroids) may not be completely reversible. However, if people can live normal lives irrespective of such sequelae, the outcome may be considered a cure. Understanding the perspectives of people with asthma is consequently essential.

Ideally, research should be directed to identifying a biomarker that indicates whether there is disease activity or a measurable physiological state, such as the absence of bronchial hyperresponsiveness, that confirms the state of being cured. For example, low levels of prostate-specific antigen at four-year follow-up is suggested as an indication of the cure of prostate cancer.[13] It is important that this definition specifies a specific antigen and when to assess its level. In asthma, normalisation of bronchodilator response or bronchial hyperresponsiveness could be the parameter for defining the absence of disease activity, or a new biomarker assessed at a predetermined timepoint. However, without such biomarkers or validated measurable physiological states, the asthma cure definition is likely to be similar to that of remission; that is, a composite outcome with several components related to various expressions of asthma that reflect disease activity, including disease manifestations (symptoms, exacerbations), physiology (lung function, bronchial hyperresponsiveness, innate immune response), and pathology (inflammation, smooth muscle remodelling). Opinions may differ about the extent of control or the combination of these factors, and different definitions are therefore likely. Importantly, however, everyone would agree that eliminating manifestations of disease should be part of the definition. Other components remain open for discussion; for example, some researchers might argue that normalising all components is required for a cure. However, the practical application of the definition would need to balance objective academic viewpoints with what is important for people with asthma.

Two proposed definitions for cure

- A biomarker or combination of biomarkers (molecular, physiological, pathological, or genetic), or a physiological state measured at a predetermined timepoint that establishes achievement of a cured state. OR:
- A combination of the following criteria:
  - Elimination of all disease manifestations, including symptoms and exacerbations, without the need for ongoing treatment for asthma for at least twelve months. This definition could be applied to all asthma endotypes, assessed using a five-item asthma control questionnaire (score below 0.75) or asthma control test (score greater than 20) on at least two occasions during the 12-month no-treatment remission period.
  - Normalisation of bronchodilator response.
  - Normalisation of underlying inflammation, bronchial hyperresponsiveness, and innate immune response. As these factors are drivers of exacerbations, normalisation is preferred, according to the asthma endotype; for example, normalisation of sputum eosinophil count in eosinophilic asthma, normalisation of sputum neutrophil count in neutrophilic asthma, and normalisation of IgE level in allergic asthma. A combination of these inflammatory markers could be required to establish a cure.
  - Stabilisation or improvement of impaired lung function and, when possible, smooth muscle remodelling. These abnormalities are typically the result of long term disease, and their reversal may be unfeasible or at least require an extended period of treatment. However, stabilisation of lung function during the 12-month no-treatment remission period would be the minimum requirement for a cure. To allow for factors that affect lung function (eg, age, sex, ethnic background, test–re-test variability), a 5–10% decline from baseline levels could be permitted. Measuring smooth muscle thickness to assess the reversal of remodelling currently requires optical coherence tomography during bronchoscopy, but surrogate measures or biomarkers could become available in the future.

We have proposed a 12-month assessment period, but many researchers and clinicians view this as too short for a complex outcome such as cure. We propose this period because the definition involves a composite outcome, and all other necessary parameters must also be met to establish a cure. Moreover, as described above, people may undergo remission on and off treatment before reaching the cure assessment period. However, the longer someone remains disease-free, the greater the likelihood that they will not experience a relapse. The disease-free predictive power of the proposed definition will need to be evaluated. The definition may also differ according to the severity of asthma. An ideal definition should establish the likelihood of asthma recurring relative to the risk of asthma developing for an age-matched group without asthma. The likelihood of relapse in a cured state would be similar to the risk of

asthma for the general population, but would be higher during remission. As there is always some risk of developing asthma for people in the general population, achieving a risk level of zero is not feasible.

Another important aspect concerns human behaviour and beliefs, as they influence adherence to therapy and the lifestyle changes required to achieve treatment goals. As the duration of treatment increases, the likelihood of non-adherence rises.[14] If a medication could deliver a cure after only a few doses, most people would probably take it as prescribed. However, when treatment must be continued for years and people progress through various stages before achieving a cure, the risk of non-adherence is substantially greater, reducing the likelihood of reaching the therapeutic goal. In any case, establishing effective therapeutic relationships between patients and clinicians is crucial. This should include education about the disease and the importance of adherence to treatment, as well as optimising asthma management skills and shared decision-making.

Directions to cure of asthma

Suboptimal treatment outcomes for people with asthma are largely attributed to the fact that many factors contribute to the clinical features of asthma, some of which are currently not modifiable. Moreover, it is unclear whether available treatments can fully normalise the pathology of asthma, such as airway remodelling. Despite evidence for disease-modifying effects of some biologics (eg, by improving lung function and reducing bronchial hyper-responsiveness and smooth muscle thickness), the durability of these effects is unclear.[15] Consequently, the quest for curing asthma should avoid limiting our approach to a single solution and embrace the multidimensionality of the problem. We must consider the possibility of different cures that target distinct domains of what is increasingly acknowledged as different asthmas. For example, the pathway to curing virus-induced asthma could be different to that for type 2-high asthma. Each pathway will have different biomarkers indicating low or absent disease activity; low levels of type 2 inflammation markers, such as eosinophils, could suffice for eosinophilic asthma, but will not be adequate for virus-induced asthma.

Conclusion

In asthma, cure can be defined as the absence of disease activity for an extended period without treatment, irrespective of the presence or absence of disease or treatment sequelae, and minimal likelihood of relapse. The definition may also encompass the physiological and pathological aspects of asthma endotypes (eg, biomarkers, bronchial hyperresponsiveness) that further ensure the cure status for each asthma type. The proposed definition needs to be evaluated in practice.

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