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PERSPECTIVE

Towards a better understanding of white syndromes and their causes on Indo-Pacific coral reefs

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Abstract Disease is increasingly recognized as a threat to coral reef ecosystems, particularly in the light of increasing anthropogenic disturbances that disrupt important symbiotic partnerships within the coral holobiont. White syndromes (WSs) are a prevalent group of coral diseases in the Indo-Pacific region that have been the focus of an increasing number of investigations over the past decade. Here, we summarize the current state of knowledge on WSs, advocate the use of established standardized criteria to describe disease lesions at gross and cellular levels to move the field forward, and highlight potential erroneous characterization of underlying causes that hinders ongoing progress in coral disease research. We argue for retention of the general term WSs for Indo-Pacific cases of tissue loss lacking distinguishing macroscopic signs and with unknown aetiologies, but erection of more specific names once standardized criteria are met. Recent advances in WS disease pathology, microbial ecology, physiology, ecology and environmental drivers are discussed and the need for greater application of interdisciplinary approaches is emphasized. Following recent widespread reports of WSs on coral reefs, a clear, concise perspective is needed to provide a focus for further research and avoid confusion in the study of this virulent group of diseases.

Keywords Coral disease · White syndromes · Indo-Pacific

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Introduction

Consistent disease descriptions and standardized diagnostic protocols are critical for the effective management of disease in animal and plant populations. However, despite increasing impacts of coral diseases on reef ecosystems worldwide, variable and even contradictory descriptions and diagnostic criteria continue to hinder research and management of coral diseases. Our understanding of the widespread group of coral tissue loss diseases, collectively known as white syndromes (WSs), has suffered from this confusion. The term WSs was first used in 1998 to describe patterns of tissue loss observed on corals in a long-term monitoring program on the Great Barrier Reef (GBR) that had commenced 6 yr prior to this first report (Sweatman et al. 2001). In order to address the difficulty of relating tissue loss diseases in the Indo-Pacific to diseases with similar macroscopic signs in the Caribbean, the term WS was subsequently adopted to describe diffuse patterns of tissue loss exposing irregular bands or patches of white skeleton on Indo-Pacific corals (Willis et al. 2004; Beeden

et al. 2008; Raymundo et al. 2008). In the Caribbean, similar macroscopic signs of tissue loss are distinguished by variable characteristics of lesion shape and rate of progression, which can be difficult to differentiate in field surveys (reviewed in Bythell et al. 2004). Following decades of research in the Caribbean, it is clear that establishing disease causation in corals is notoriously difficult (Bythell et al. 2002), which partly explains the current proliferation of names for white diseases in the Caribbean (e.g. white band I and II, white plague I, II, and III, white pox), each with potentially different causative agents (Bythell et al. 2002; Bruno et al. 2003; Lesser et al. 2007). Indo-Pacific WSs are similarly likely to have different and/or multiple factors influencing disease initiation, manifestation and progression (Bourne et al. 2009; Work and Aeby 2011). In recognition of the likelihood that it will take substantial time and resources to identify factors causing WSs, it was suggested that the most prudent approach for field studies of coral disease is to refer to patterns of tissue loss of unknown aetiology on Indo-Pacific corals collectively, rather than to erect a variety of names for macroscopic signs that are difficult to distinguish in the field (Willis et al. 2004). Almost a decade after the term was first coined, and despite many advances in our understanding of coral diseases, problems with identifying causes of coral diseases in general (Lindrop et al. 2008; Rodgers 2010), and WSs in particular, continue to justify the use of this collective term to describe unexplained patterns of coral tissue loss on Indo-Pacific corals.

Multiple factors have contributed to the slow rate of progress in the field of coral disease research. The lack of rapid, accurate diagnostic tools for coral diseases (Pollock et al. 2011) means that lesions are typically characterized based on underwater observations of macroscopic features, particularly lesion colour, patterns and extent of tissue loss, and characteristics of exposed coral skeleton. Not unexpectedly, this has led to ambiguous classifications of coral diseases that are largely open to interpretation. Difficulties in replicating the reef environment within laboratory studies, combined with plasticity of microbial associations within the coral holobiont in experimental settings (Ainsworth and Hoegh-Guldberg 2009), have further hindered the development of systematic approaches to teasing apart potential factors contributing to disease causation. Standard criteria for characterizing the morphology of coral lesions at the gross level have been disseminated (Work and Aeby 2006; Work et al. 2008), and such approaches are routinely used to tease apart disease causation in other animal systems (Work and Meteyer 2014). Until these standard criteria for disease identification are uniformly embraced, ambiguity in the field of coral disease research will persist, impeding the development of comparative frameworks needed to better define various types of WSs and aid the identification of their corresponding causative agents (Work and Aeby 2006; Ainsworth et al. 2007b; Work et al. 2008; Downs et al. 2009; Rodgers 2010). Here, we review the status of WSs on Indo-Pacific reefs, outline the challenges hindering research on WSs, and suggest potential approaches to further our understanding of this elusive group of diseases.

White syndromes of the Indo-Pacific: a cautionary note on the emerging proliferation of disease names

The first report of an Indo-Pacific WS was published by Antonius (1985), who noted linear tissue loss progressing over colonies with a clear interface between living coral tissue and brilliant white skeleton. Originally called white band disease (WBD), this pattern of tissue loss clearly falls within the definition of WS (Table 1). This early record describes WSs on Philippine reefs affecting over twenty coral species, predominantly in the family Acroporidae (Antonius 1985). Subsequently, WSs were reported to affect 17 species/growth forms of corals from a range of important reef-building families on the GBR, particularly fast-growing, tabular, and branching species in the families Acroporidae and Pocilloporidae (Willis et al. 2004). Tissue loss diseases, consistent with the definition of WSs, have now been reported from most reef regions throughout the Indo-Pacific (e.g. Raymundo et al. 2003; Timothy et al. 2004; Work and Rameyer 2005; Ainsworth et al. 2007b; see Table 1). Localized WS outbreaks have also been reported to affect a range of species over a wide geographic range (Table 1; Fig. 1), including: the tabulate coral *Acropora cytherea* on reefs in the remote North-Western Hawaiian Islands (Aeby 2005); tabulate species of *Acropora* in the Marshall Islands, where outbreaks have resulted in extensive mortality over a number of years (Jacobson et al. 2006); tabulate species of *Acropora* at Christmas and Cocos Islands, North Western Australia (Hobbs and Frisch 2010); species of *Pachyseris* in Palau (Sussman et al. 2008; Page et al. 2009); and species of *Acropora*, *Montipora*, *Pocillopora*, *Goniastrea*, *Platygyra* and *Porites* on reefs of the US remote Pacific Islands (Vargas-Angel 2009; Aeby et al. 2011).

A number of Indo-Pacific diseases with macroscopic signs consistent with WS have been assigned distinct names in line with developed comparative frameworks (Work and Aeby 2006; Work et al. 2008). For example, a tissue loss disease termed *Montipora* white syndrome (MWS) was identified on reefs in Hawaii (Aeby et al. 2010), and subsequent studies have identified both acute and chronic versions based on differences in the rate of lesion progression (Work et al. 2012). Another tissue loss

Table 1 Descriptions of Indo-Pacific white syndromes

Lesion description	Disease name	Reported geographic locations	Corals affected	Representative reference
Diffuse white syndromes: tissue loss revealing band of white skeleton; peripheral, basal or central locations; affects polyps and coenosarc. Often originating from a small lesion front and spreading to a band front across the entire colony. Lesions have a linear shape and diffuse border resulting in a continuous pattern of white exposed skeleton. Progression rate is moderate (subacute) to rapid (acute)	White syndromes (WSs)	Great Barrier Reef, Australia, USA, Pacific remote Island areas, Guam	Families: Acroporidae, Poritidae, Pocilloporidae, Agariciidae and Faviidae	Willis et al. (2004), Vargas-Angel (2009), Myers and Raymundo (2009)
	Acropora white syndrome (AWS)	Northwestern Hawaiian Islands, Marshall Islands, Watakobi Marine Park, Indonesia, American Samoa, North Western Australia, Palmyra Atoll, Japan	*Acropora* spp.	Aeby (2005), Jacobson et al. (2006), Haapkyla et al. (2007), Aeby et al. (2008), Hobbs and Frisch (2010), Williams et al. (2011), Weil et al. (2012)
	Atramentous necrosis	Magnetic Island, Australia	*Montipora aequituberculata*	Jones et al. (2004), Anthony et al. (2008)
	Australian subtropical white syndrome (ASWS)	Solitary Islands, Australia	*Turbinaria mesenterina*	Dalton and Smith (2006)
	Montipora white syndrome (MWS)	Hawaii	*Monitpora capitata*	Aeby et al. (2010)
	White band disease	Philippines Red Sea	Acroporidae, Pocilloporidae, Agariciidae and Faviidae	Antonius (1985)
	White plague disease	Red Sea, Thailand	*Favia* spp., *Goniastrea* spp. *Pavona duerdeni*, *Porites lutea*	Barash et al. (2005), Roder et al. (2014)
	Porites white patch syndrome (PWPS)	Western Indian Ocean	*Porites lobata* and *Porites lutea*	Séré et al. (2012)
	Porites tissue loss (PorTL)	Hawaii	*Porites* spp.	Williams et al. (2011)
	Porites bleaching with tissue loss (PBTL)	Hawaii	*Porites compressa*	Sudek et al. (2012)
Focal white syndromes: May start as white tissue discolouration leading to full tissue-thickness ulceration; focal or multi-focal; typically central location but may be anywhere on colony; affects polyps and coenosarc. Multifocal lesions often coalesce and appear as circular to oblong on coral colonies. Lesions may have a smooth or diffuse border. Lesion size is small (~3–5 mm diameter) and can have varying rates of progression from chronic (not progressing) to subacute (moderate progression rate)	Porites ulcerative white spot disease (PUWS) focal (includes UWS/PUWS)	Philippines, Wakatobi Marine Park, Indonesia, Japan	*Porites* spp. (branching and massive)	Raymundo et al. (2003), Raymundo et al. (2005), Haapkyla et al. (2007), Weil et al. (2012)
	Ulcerative white spot disease (UWS)	Philippines	*Montipora*, faviids, and the octocoral *Heliopora*	Raymundo et al. (2008)

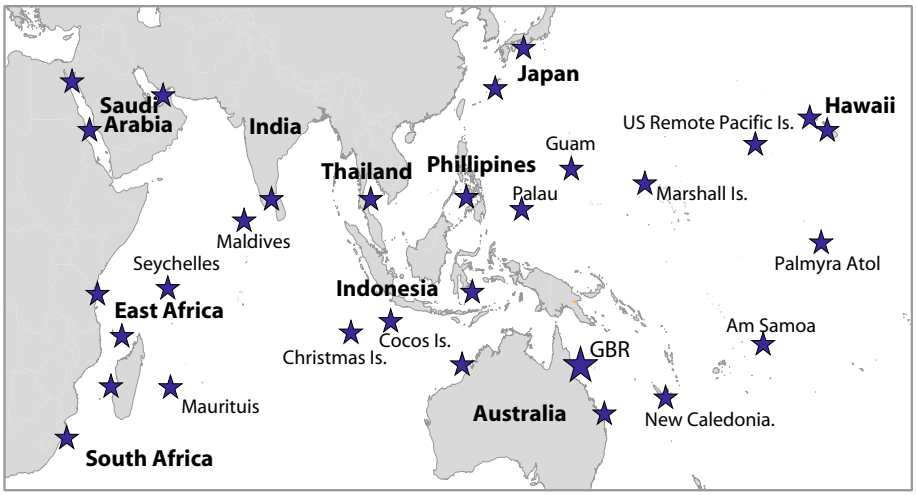

Fig. 1 Map showing locations throughout the Indo-Pacific where WSs have been reported

disease that progresses more rapidly in summer than in cooler months, and which affects thirty-three coral species from six families, has been described from Australian temperate reefs and called Australian subtropical white syndrome (ASWS; Dalton and Smith 2006; Dalton et al. 2010). There is merit in providing detailed descriptions of these disease states; however, investigators that observe tissue loss on these coral genera and species in other reef regions are now faced with the dilemma of selecting the most appropriate name in the absence of definitive aetiologies.

A proliferation of names for Indo-Pacific WSs has recently emerged, similar to the proliferation of names that now exist for Caribbean white diseases (reviewed in Bythell et al. 2004). For example, Séré et al. (2012) reported a disease from the Western Indian Ocean that affects massive colonies of *Porites lobata* and *P. lutea* and introduced the name *Porites* white patch syndrome (PWPS) (Table 1). At this stage, there are no histological or etiological details that distinguish PWPS (see Séré et al. 2013) from the more general case of WS (see similar photo in Beeden et al. 2008, Sect. 3b WSs), or specific morphological criteria that can be used to confidently assign this name to signs of tissue loss on colonies of *Porites*. In addition, *Porites* tissue loss (PorTL) has been introduced to describe irregular patches of tissue loss with unknown aetiologies on *P. compressa* (Williams et al. 2010), and more recently, *Porites* bleaching with tissue loss (PBTL) has been introduced for grossly similar macroscopic signs that follow an initial bleaching stage on the same species (Sudek et al. 2012; Lawrence et al. 2014). We recommend that all these disease cases be termed *Porites* WS, using the coral genus name as an additional layer of unambiguous information, until the underlying aetiologies of each disease are determined.

Furthermore, the Caribbean term white plague disease continues to be applied to cases of tissue loss on Indo-Pacific reefs (e.g. Barash et al. 2005; Roder et al. 2014), without clear evidence that field signs or potential causative agents are consistent with white plague I, white plague II, or white plague III. In the Caribbean, white plague II has been associated with *Aurantimonas coralicida* (Denner et al. 2003), but recent studies of bacterial communities associated with white plague-like tissue loss on reefs in the Red Sea (Thompson et al. 2006) and at Koh Tao, Thailand (Roder et al. 2014), have not detected this pathogen. To the contrary, a new causative agent, *Thalassomonas loyana* sp. nov., has been identified for white plague-like tissue loss in Red Sea corals (Thompson et al. 2006), highlighting the pitfalls of applying names erected for Caribbean diseases to Indo-Pacific diseases. This proliferation of distinct names for macroscopically similar disease signs, which often lack defined, distinguishable aetiologies, leads to confusion among reef researchers and managers looking to consistently identify the diseases they encounter.

In some cases, new diseases reported from the Indo-Pacific region have macroscopic signs consistent with the general WS signs of tissue loss exposing white skeleton, but also have distinctive lesion shapes, patterns, and progression characteristics that have been clearly described, setting them apart and warranting the erection of a specific name. For example, a multifocal pattern of tissue loss exposing small circular areas of bare white skeleton, which was first described from lesions on *Porites* found on reefs in the central Philippines, was named *Porites* ulcerative white spot disease (PUWS) (Raymundo et al. 2003). The characteristic progression of PUWS lesions, from discrete, bleached, round foci that often coalesce and occasionally cause whole colony mortality (Raymundo et al. 2003), further supports the need for a specific name for this suite of disease signs. However, discovery of similar lesions on species of *Montipora*, faviids, and the octocoral *Heliopora* has led to the name being modified to a more general version, ulcerative white spots, to accommodate the additional range of coral hosts (Beeden et al. 2008; Raymundo et al. 2008). As another

Table 2 Identified challenges and solutions in identifying WS disease causation

Selected key challenges in the coral system	Associated issues	Proposed solution
Confused and/or conflicting descriptions at the level of gross lesions are still common in the coral disease literature	Regional comparisons of diseases are difficult if standardized descriptions of lesions at the gross level are not followed	When documenting reef health in reef-wide surveys, it is important that clear and easily identifiable criteria are used to describe modes of coral mortality. Coral disease researchers need to embrace standard criteria for characterizing coral lesions at the gross, microscopic, immunological, and microbial level (as outlined in Work and Aeby 2006; Raymundo et al. 2008; Work et al. 2008). Where possible, the genus of the coral colonies affected can be added to the disease name, thereby adding an additional layer of unambiguous information; for example, current accepted disease names include "*Montipora* white syndrome" and "*Acropora* white syndrome"
Macroscopic criteria characterizing lesions provide a base description of apparent colony health at a single point in time and are not necessarily indicative of the lesion initiation, causation or progression	It is often extremely challenging to identify the earliest stages of lesion initiation on corals. Therefore, sampling of coral lesions may occur well after initial lesion onset and represent a late stage progression, thus secondary colonisers of compromised coral tissue may be confused with primary agents	Any disease investigations should incorporate detailed ecological surveys, documenting disease abundance, prevalence and spread through a population. At the individual coral colony level, lesion progression should also be mapped across the coral colony. Good ecological information of disease within a population will provide the best opportunity to sample lesions at a time when causative agents are associated with an actively progressing lesion
Linking a causative agent with rigorous lesion descriptions at the morphological (gross), cellular and microbial levels	Often bacterial causation is based on gross lesions replicated experimentally, though comparisons of lesions at the cellular level identifying similar bacterial agents in both experimental trials and field-based studies are lacking	Controlled experimental studies demonstrating bacterial aetiologies need to be closely linked with histological evidence for microbial invasions or causative effects resulting in distinctive lesions both with experimental and field-based studies (as emphasized strongly in Work et al. 2012)
Hard calcium carbonate structure results in challenges for processing samples to investigate scleractinian coral samples at the cellular level	The hard calcium carbonate structure of corals results in decalcifying steps prior to the application of cellular approaches such as histology and fluorescent in situ hybridization (FISH) to characterize lesions. These decalcifying steps can disrupt cellular structure and associated organisms, making it difficult to link causative agents with the lesion	Investigating the cellular response of the coral using standardized histological methods should ensure correct embedding of samples to prevent excessive tissue disruption during decalcification. However, developments in histological preparation of coral samples that do not require decalcification allow systematic investigation of cellular responses and avoid disruption of cellular structures (Kawamoto 2003). Such novel techniques will greatly aid efforts to link cellular responses with biotic causative agents
Scleractinian corals are comprised of a complex symbiosis between the animal and it algal dinoflagellate partner (*Symbiodiuim*). This intimate relationship means that the cellular response of both partners to disease needs to be understood. In addition, recent research has highlighted how other microbial partners, including Bacteria, Archaea, Fungi, and even viruses are central to the fitness of the complete holobiont	Corals represent a symbiosis among an animal (the coral host), an alga (endosymbiotic dinoflagellate *Symbiodinium*), and various microbial associates; therefore, understanding the response of the holobiont can be challenging. To achieve this, a multi-disciplinary approach is required, combining traditional biomedical approaches with developing genetic- and immunological-based methodologies. Apart from accommodating these additional complexities, the approach for diagnosing coral disease should be no different to approaches routinely undertaken in any number of human and animal disease applications	To understand disease within corals, an in-depth knowledge of the basic biology of each holobiont member is required. Genomics-based approaches (genomics, metagenomics, metatranscriptomics) are currently being applied to study corals and their microbial associates, which should provide this basic information. However, model systems are required (*Symbiodinium* cultures and coral animal models) that can tease apart the complex interaction of host and dinoflagellate partner and help investigate the disease response of each partner in isolation and as part of the holobiont. Additionally, results derived from molecular-based approaches must always be mapped back onto what is happening at the cellular level. A deductive approach is recommended, where both infectious and non-infectious causes of diseases are considered. Field ecology and disease history needs to be coupled with cellular morphology of lesions at the microscopic level, which can then guide additional evidence-based approaches, including genetics, proteomics, toxicology, and immunological investigations. These approaches can be performed in parallel with attempts to replicate lesions experimentally and understand disease pathogenesis, thereby fulfilling Koch's postulates. However, the causative agent identified must be confirmed at the cellular level, both in the experimental trials and field-based lesions

Table 2 continued

Selected key challenges in the coral system	Associated issues	Proposed solution
The current understanding of coral immunology is rudimentary, especially with respect to defences against infectious agents. Although some key innate immune pathways have been identified (e.g. prophenoloxidase-activated melanization response and basic oxidative pathways), there is large scope for further critical discoveries	An extensive knowledge of immune responses has been invaluable in understanding pathogenesis in countless other animal disease case examples. Identifying the underlying cellular immune responses of corals and their algal partner (independently and in symbiosis) to abiotic and biotic challenges should be a research priority	Emerging genomic-based approaches will provide valuable information for identifying the key immune response pathways in corals and *Symbiodinium*. Using this information and translating it into standardized models for investigating cellular responses to biotic and abiotic challenges leading to disease will be difficult but essential. Combining studies on *Symbiodinium* cultures and coral animal models with diagnostic tests on gene expression, protein activities, and overall immune cellular response of the coral holobiont would provide a significant step forwards in understanding disease drivers

example, disease signs that presented as blackened spreading lesions on corals on a fringing reef at Magnetic Island in the central inshore section of the GBR were assigned the name atramentous necrosis (Jones et al. 2004). Subsequently, however, a number of stages in the progression of the disease were identified, with the initial stage consistent with WS lesions (Anthony et al. 2008) and the characteristic greyish black lesions representing a secondary microbial community (Bourne 2005). Nevertheless, the distinctiveness of the greyish black lesions, reflecting a white film overlying black deposits, combined with the presence of similar lesions on species of several other coral genera, including *Acropora*, *Echinopora*, *Merulina,* and *Turbinaria* (Beeden et al. 2008; Raymundo et al. 2008), supports the maintenance of atramentous necrosis as an appropriate name for lesions presenting with these macroscopic signs.

Predation scars represent another potential source of confusion for field-based studies of WS diseases. A range of vertebrate and invertebrate corallivores produces feeding scars that resemble either focal patterns of tissue loss characteristic of ulcerative white spots or more diffuse, irregular patterns of tissue loss characteristic of WSs. For example, feeding by the spotted coral blenny *Exallias brevis* produces round bare patches of exposed skeleton that could be mistaken for ulcerative white spots, and feeding by the gastropod *Drupella* can produce diffuse bands of exposed skeleton that could be mistaken for irregular, diffuse WSs. On the other hand, lesions can be attributed to potential vertebrate or invertebrate corallivores seemingly associated with the lesion, when the role of the associated organism is quite different. For example, predation by the crab *Cymo melanodactylus* was proposed to cause WS-associated tissue loss on tabular species of *Acropora* in the Chagos Archipelago based on in situ observations of crabs aggregated along borders of WS lesions (Pratchett et al. 2010, 2013). However, recent experimental studies show that *C. melanodactylus* crabs actually slow WS lesion progression and thus appear to debride WS lesions rather than progress them (Pollock et al. 2013). Although the presence of an assumed predator near a lesion is useful evidence for suggesting predation-induced tissue loss (Raymundo et al. 2008), recent confusion over the role of *C. melanodactylus* crabs in WS causation highlights the need for stronger evidence than simple correlation to assign disease causation. A decision tree for distinguishing WSs from other causes of tissue loss, such as predation (Beeden et al. 2008; Raymundo et al. 2008), is available and should be applied as standard best practice. The decision tree distinguishes characteristic patterns of tissue loss caused by predation from disease signs. For example, extensive areas of recently exposed white skeleton and scalloped lesion borders typical of crown-of-thorns starfish scars can be distinguished from narrow, linear

bands of recently exposed skeleton and diffuse lesion borders typical of WSs on tabular species of *Acropora*.

A further complicating factor is that diseases that are typically separable from WSs based on macroscopic criteria can be confused with WSs in some cases. For example, brown band disease (BrB) typically has a characteristic brown mass of ciliates at the lesion border, and the presence of visible concentrations of protists or epilithic fauna at the advancing lesion boundary is typically diagnostic of a non-WS pathology; however, low ciliate densities can confound the distinction between BrB and WS during in situ coral health assessments (Willis et al. 2004). One recent study comparing WS and BrB lesions on branching species of *Acropora* at Heron Island and the Solomon Islands found similar ciliate- and coral-associated bacterial communities and concluded that these diseases represent the same syndrome (Sweet and Bythell 2012). However, care should be taken in generalizing from a limited number of cases, and we stress that WS lesions may be caused by multiple factors. Similarities or differences in microbial and epilithic communities on a few species at discrete locations are not sufficient to confirm shared disease causation across the Indo-Pacific. Although it is likely that all progressing lesions examined in this study were attributable to brown band ciliates, this does not warrant synonymizing brown band disease with the more general category of WSs, which may have a number of causative agents.

Tackling the challenge of determining white syndrome causation

Studies of environmental factors associated with increased prevalence of WSs on Indo-Pacific coral reefs have produced apparently conflicting results. For example, patterns of WS abundance on the GBR were first correlated with warm thermal stress on reefs with high cover of coral hosts (Bruno et al. 2007; Heron et al. 2010; Maynard et al. 2011). Strikingly, a 20-fold increase in the abundance of WSs was recorded following anomalously warm temperatures in 2001–2002 (Willis et al. 2004; Bruno et al. 2007). Modelling studies have also indicated that cold winters can reduce the likelihood of WS outbreaks, potentially by reducing pathogen loads (Heron et al. 2010). However, it has also been shown that periods of cold seawater temperature (cold snaps) correlate with increasing probability of WS occurrence (Roff et al. 2011; Ban et al. 2012). These long-term trends on the GBR reflect the difficulties associated with characterizing macroscopically similar, but potentially etiologically distinct diseases even within a single geographic region.

Detailed histological studies indicate the presence of multiple host responses associated with WSs, including apoptosis-induced tissue loss in species of *Acropora*, potentially in response to a causative agent or environmental stress (Ainsworth et al. 2007a, b; Work and Aeby 2011). Additionally, the dominant Hawaiian coral *Montipora capitata* may exhibit either rapidly progressing (acute) lesions (MWS) associated with ciliates and display signs of necrosis, or slowly progressing (chronic) MWS lesions associated with helminths or chimeric parasites and display signs of wound repair (Work et al. 2012). The complexity of the WS group of diseases is further highlighted by a recent report detailing the ability of a newly identified marine pathogen *Vibrio owensii* to induce MWS tissue loss in *Montipora capitata* corals in Hawaii (Ushijima et al. 2012). This is in contrast to earlier microbiological and molecular studies that identified other bacterial pathogen(s), including *V. coralliilyticus* and *V. harveyi*, as causative agents of some WS cases (Luna et al. 2007, 2010; Sussman et al. 2008). Rather than viewing these studies as contradictory, it is more reasonable to view them as mounting evidence that WSs can have multiple causes. It is unreasonable to expect that one mode of pathogenesis could explain all types of tissue loss (both rapid and slow manifestations) of unknown origin across all Indo-Pacific reef regions.

Multiple issues confound current approaches used to investigate causation of WS diseases. For example, disease causation is often inferred from aquarium-based bacterial infection challenges that experimentally produce gross disease lesions similar to those of a known coral disease. Definitive attribution of disease causation, however, will require putative bacterial pathogens identified in aquarium-based infection experiments to be successfully localized at the cellular level within field-derived disease samples. Additionally, molecular-based bacterial community profiling techniques are often used to infer "potential pathogens" within WS samples, based solely on retrieved 16S rRNA genes that demonstrate high sequence similarities to other known pathogens. While bacterial community profiling is valuable for assessing community structure and identifying microbial shifts, disease causation cannot be attributed to specific bacterial species and strains based on this technique alone.

Progress in the development of effective approaches for the study of WSs and their causes on Indo-Pacific reefs will be expedited if we build on knowledge developed for other animal groups. Standardized criteria for disease characterization have proven to be extremely useful in other animal systems and involve field-based investigations, microscopic-based pathology approaches, laboratory investigations to detect the causative agent(s), and infection trials to satisfy Koch's postulates (Bower et al. 1994; Lightner 1996; Lightner and Redman 1998; Wobeser 2010). Although these approaches have been used in coral

disease investigations, they are often undertaken in isolation and without integration, thereby providing a partial or incomplete picture of the disease pathology (Work and Meteyer 2014). It is true that unique characteristics of corals, such as their hard external skeletons and lack of standard animal models, pose a number of challenges to studies of disease causation (outlined in Table 2). However, rigorous application of comprehensive, established diagnostic methodologies combined with the development of genomics-based approaches (e.g. detailing the immune system and microbiome of the coral holobiont) and targeted investigations employing appropriate and stringent experimental designs still constitute the most effective approach to begin teasing apart complex interactions between the environment and causative agents of WSs (Table 2).

The application of approaches developed in biomedical and veterinary science to systematically describe coral lesions (Work and Aeby 2006) provides an important starting point for investigating WS causation. Disease lesions that display different macroscopic signs must be carefully separated by observable differences using available classification frameworks (Work and Aeby 2006; Beeden et al. 2008; Raymundo et al. 2008). Ideally, rigorous descriptions at the gross morphological, cellular and microbial levels should accompany disease descriptions (Work and Aeby 2006; Work et al. 2008; Bourne et al. 2009). As Work et al. (2012) highlight, controlled experimental studies demonstrating bacterial aetiologies must be closely linked with histological evidence of bacterial invasions or causative agents that result in distinctive lesions. The complex and dynamic nature of the coral holobiont must also be considered in both experimental and field studies, which will require a deeper understanding of coral cellular biology, as well as of coral immune responses to environmental stress and microbial challenge. In addition, greater knowledge of the functional roles of coral-associated microbes within coral microhabitats is required, particularly how potential microhabitat-specific microbial associations change in response to environmental stress. The critical role of microbes in the health of organisms, ranging from corals to humans, has become increasingly clear in the last few years (Turnbaugh et al. 2007; Bourne et al. 2009; Ainsworth et al. 2010; Cho and Blaser 2012) and represents an important area for future research in corals. Once baseline understanding of WSs and their causes is established, regional comparisons will enable disease pathologies to be accurately grouped, defined, and categorized. However, in the absence of such information, disease lesions characterized by tissue loss without distinguishing macroscopic signs (Table 1) should be grouped under the general category of WSs.

Developing an effective approach for naming and investigating white syndromes

There is an urgent need for a coordinated body of researchers and specialists in Indo-Pacific coral diseases that could evaluate proposals for erecting new names for Indo-Pacific diseases, including for Indo-Pacific tissue loss syndromes. Ideally, such a body would evaluate proposals against a standard set of criteria. A newly established Action Network for Coral Health and Resilience (ANCH&R) in the Indo-Pacific (Wilson pers comm) would be a useful starting point for developing such a coordinated body of experts. We also highlight the dire need for greater cross-disciplinary interactions between ecologists, microbiologists, immunologists, cell biologists, animal pathologists, and geneticists to address complex issues and knowledge gaps associated with understanding coral diseases such as WSs and to identify their causative agents. Coral disease investigations often provide only part of the story and lack a holistic, integrative understanding of the host, causative agent and environmental conditions that lead to observed disease signs. Although such multi-disciplinary studies are time consuming and challenging, they will provide the best approach for definitive identification of disease causation. The establishment of shared, open access tissue depositories and online resources for accurate comparison of macroscopic, microscopic, physiological, and microbial characteristics of WSs, in both field and aquaria studies, is also necessary to further advance our ability to characterize and understand this prevalent group of diseases. These approaches must be adopted rapidly in order to understand and potentially manage increasing levels of coral disease that continue to contribute to worldwide coral reef ecosystem declines.

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