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MINIREVIEWS

Review of allergic contact dermatitis: Scratching the surface

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Abstract

Contact dermatitis-including allergic contact dermatitis (ACD)-n and results in over four million lost work days per year in the United States alone. ACD is a classic example of a type IV delayed hypersensitivity reaction, and represents a significant burden on the health system, economy, and patient quality of life. Thorough history taking, clinical examination, histologic evaluation, and patch testing are keys to diagnosing contact dermatitis. Patch testing, especially with comprehensive and customized panels based on the patient's exposure history, is particularly useful in identifying potential allergens in the case of allergic contact dermatitis. ACD management requires a combination of direct medical intervention, patient education, and appropriate environmental modification to prevent exposure to offending allergens in the home or workplace. Continuing advances in the study of ACD has led to an increased understanding of the disease processes, new methods for diagnosis, and improved management. This article reviews ACD-aiming to connect recent investigational data with the current clinical understanding of disease pathophysiology, diagnostic techniques, and management strategies.

Key words: Allergic contact dermatitis; Occupational dermatitis; Skin sensitization; Contact allergens; Patch testing

Core tip: Allergic contact dermatitis (ACD) affects approximately 20% of the adult population and results in over four million lost work days per year in the United States. Continuing advances in the study of ACD have led to an increased understanding of the disease processes, new methods for diagnosis, and improved approaches for treatment. This article discusses ACD holistically, aiming to connect recent investigational data with current clinical understanding to review disease pathophysiology, diagnostic techniques, as well as management strategies.

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INTRODUCTION

Contact dermatitis (CD) is a common inflammatory skin

reaction that follows direct contact of substances with the skin[1,2]. Contact dermatitis affects approximately 20%[3,4] of the adult population and is responsible for over eight million outpatient visits to dermatologists per year in the United States alone[5]. Occupational related CD represents 90% of all occupation related skin disorders and results in over four million lost work days per year[6,7]. CD represents a significant burden on the health system, economy, and patient quality of life[4,7,8].

Contact dermatitis is divided into two distinct disease processes: irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). ICD is characterized by solitary or cumulative exposure to irritants (both chemical and physical) that induce direct keratinocyte damage and local inflammation, regardless of prior exposure[2,4]. In contrast, ACD is an example of type Ⅳ delayed-type hypersensitivity, which is divided into distinct phases: sensitization, elicitation, and inflammatory regulation[2,4,9,10]. Sensitization is the immunologic priming response following the initial topical exposure of a chemical allergen. Subsequent exposures at the same or distant sites on the skin result in a more vigorous secondary immune response at the point of contact, referred to as elicitation[1,4]. The extent and severity of these hypersensitivity responses are controlled by underlying inflammatory regulation pathways. The clinical presentation of these phases is referred to as ACD[4]. Continuing advances in the study of ACD have led to an increased understanding of the disease processes, methods for diagnosis, and approaches for treatment. This ACD review article will aim to connect investigational data with current clinical understanding to review disease pathophysiology, diagnostic techniques, as well as management strategies.

MECHANISM OF ACD

ACD is a multifactorial disease, resulting both from genetic and environmental factors[2,5]. ACD is characterized as a type Ⅳ delayed hypersensitivity reaction[10]. Once one or more potential allergens come in contact with the skin, a series of phases-sensitization, elicitation, and inflammatory regulation-occur that lead to an inflammatory response to the allergen(s)[1,2,5,9]. The precise roles these phases play in ACD are still under investigation. ACD in humans typically develops in response to repeated subthreshold exposures to contact allergens with clinical signs and symptoms of dermatitis developing gradually overtime[5,9]. Interestingly, our current understanding of ACD pathophysiology is primarily based on animal studies using the contact hypersensitivity (CHS) model[5,10]. In CHS studies, potent lipophilic compounds are applied directly to a rodent's skin. This serves as the sensitization phase. Five to seven days later the same compound is applied to a different location, resulting in the elicitation response. Given the short time course and potency of compounds used for priming an immunologic response, the CHS model depends on innate inflammatory mechanisms more than ACD. Regardless, it requires T cell antigen specific response, and is recognized as an analogous delayed-type IV hypersensitivity reaction[5].

For a cutaneous immune response to be induced, contact allergens must be able to penetrate the stratum corneum, the water impermeable outer layer of the skin, in order to gain access to the deeper living layers of the epidermis[1,4,11]. Filaggrin proteins are critical for maintaining epidermal homeostasis, aiding in the alignment of keratin filaments in the corneocytes and hydration of the stratum corneum[10]. Without these proteins, there is impaired skin barrier function, allowing for easier penetration of chemical irritants and allergens. Patients with a history of atopic dermatitis and filaggrin mutations have an increased risk, four to seven fold, of developing contact dermatitis[12].

Contact allergen characteristics also play a critical role in developing ACD. Most contact allergens are small organic chemicals or metal ions with molecular weights of < 500 daltons and lipophilic residues. These compounds are small enough to reach the horny layer of the epidermis, but too small to be immunogenic on their own[1,4,10]. Allergen sensitization potential depends on forming stable reactions with proteins and creating hapten-protein conjugates[4]. Sensitizing metals (*e.g.,* nickel, chrome, cobalt, *etc.*) react readily to form stable non-covalent protein-metal complexes. However, a majority of contact allergens cannot bind directly to host proteins and require either environmental or direct enzymatic changes in order to transform into reactive metabolites capable for forming covalent bonds[2,9,10,13]. Allergens that undergo activation from the external environment such as photosensitizers with ultraviolet radiation or auto-oxidizing agents such as the fragrances D-limonene or linalool are referred to as pre-haptens. Alternatively, allergens that are modified through the natural detoxification processes of keratinocytes (*e.g.,* cytochrome P450 isoenzymes, UDP glucuronosyltransferase, glutathione S-transferase, *etc.*) into highly reactive intermediates are termed pro-haptens[14]. Some familiar pro-haptens include natural products (urushiol), dyes (paraphenylene diamene, disperse blue), fragrances (eugenol), drugs (sulfamethoxazole), and industrial chemicals (styrene, ethylenediamine)[1,13]. Once haptenated proteins are formed, they activate an inflammatory cascade attracting dendritic cells (DCs) to the contact site[2]. Haptens are phagocytosed by DCs triggering the first phase of ACD, sensitization[1].

As part of the sensitization process, the protein-allergen complexes are broken down and expressed as peptide epitopes on the grooves of MHC class Ⅰ and Ⅱ molecules. These antigen bearing DCs migrate from the initial contact site to regional lymph nodes where $CD8^+$ and $CD4^+$ T-lymphocytes in the paracortex are primed. Here T-cells undergo differentiation into effector T-helper (Th) cells, cytotoxic T-cells, and

Table 1 Key points in allergic contact dermatitis history taking[18-20]

Topic	Details
Demographics	Age, sex, race, ethnicity
Past medical history	Personal history of atopic dermatitis, asthma, allergic rhinitis or other allergic diseases, co-morbidities, current medications, and medical device implantation (including dental implants such as braces, crowns, or fillings)
Family history	Atopic dermatitis, allergic rhinitis, or asthma
Occupational history	Current job description, materials handled at work, type and regularity of chemical exposures, previous employment history, and symptoms at work
Dermatitis specific history	Initial rash: date/duration, area(s) affected, symptoms, pattern/progression of eruption, frequency of recurrence, and treatments attempted Current rash: areas affected, severity, and changes during work week vs weekend
Home environment	Location (urban, suburban, or rural), pets (Dogs, cats, birds, rodents, livestock, *etc.*), house cleaning activities, and detergents used
Personal care	Hand washing frequency, deodorant, lotion, cream, perfume/cologne, hair styling aides, nail polish remover, makeup use, *etc.*
Sports/hobbies	Type of equipment used, indoor vs outdoor, and symptoms with activity
Jewelry/piercing/tattoos	Type, location and frequency of jewelry use, type and location of piercings, history of temporary or henna based tattoos

T-regulatory (Treg) cells, which over the course of weeks to months begin to circulate into the peripheral blood[2,5,10].

Future re-exposure to sensitized contact allergens are recognized by DCs and result in a vigorous immune response (elicitation) and a classic inflammatory rash typically within 12 to 72 h[4,9]. Resolution and regulation of the inflammatory response involves clearance of haptens and activation of $CD4^+$ regulatory T cells[2,5,10]. Studies have found haptens may remain in the for skin weeks to months following the initial exposure, suggesting the importance of anti-inflammatory cytokine production from local skin cells in addition to regulatory cells[15]. While their precise action remains unknown, increasing evidence suggests $CD4^+$ Treg cells control the priming and expansion of hapten specific $CD8^+$ cells in the skin[16]. Other mechanisms, including MicroRNA have been found to have a regulatory component[17]. MircoRNA segments bind to sections of inflammatory sequences of mRNA, blocking and thereby inhibiting their effective translation. The accelerated turnover and breakdown of the transcripts alters gene expression and likely contributes to the dysregulation of inflammation in allergic contact dermatitis[17].

DIAGNOSIS

Timeliness of diagnosis for ACD is essential for improved outcomes in the management of this disease. Making a diagnosis of ACD entails the following steps: (1) detailed history; (2) suggestive physical exam findings; (3) supportive histological evidence, and (4) patch testing[3].

Clinical history and physical

Recognizing the clinical symptoms, exposure history, morphology, and distribution of lesions are important in the diagnosis of ACD. The first step in diagnosis is a obtaining a detailed history in order to determine the clinical relevance of various patch test allergens. This may require extensive questioning. Standardized screening questionnaires are helpful to ensure comprehensive data collection regarding demographics, past medical history, family history, occupational history, home environment, hobbies, jewelry, tattoo use, use of personal care products, disease course and response to previous treatments (see Table 1 for key topics and relevant details to discuss when screening patients for ACD)[18-20].

Many ACD cases can be traced to occupation[20]. Certain professions-*e.g.,* health professionals, construction/factory workers, machinists, cooks, janitors, farmers, hair dressers, among others-have an increased risk of developing occupational ACD[21]. However, exposure to common industrial allergens, including cements, glues, plasters, and solvents, may also occur at home[20]. Gathering a history should include information about temporality (*i.e.,* when do symptoms worsen or improve) and location (*i.e.,* where is the patient when symptoms worsen or improve)[22]. For example, if symptoms improve on weekends or vacations, it suggests occupational relation. In contrast, symptoms that worsen during holidays or weekends may indicate recreational exposure to allergens.

Physical exam also provides important diagnostic clues. While dermatitis can have various morphologies, lesions typically present acutely as erythematous, edematous, or urticarial appearing papules, plaques, vesicles and bullae that become increasingly eczematous and weeping[18,23]. In areas with thinner skin (*e.g.,* eyelid, penis, and scrotum), lesions are more edematous, with fewer superimposed vesicles[18,23]. Intense pruritus leads to secondary changes of excoriation; subsequent impetiginization may also be observed. With persistent or repeated exposure, sub-acute or chronic ACD may develop. In sub-acute ACD, the skin remains erythematous and edematous as vesicles are replaced by erosions, oozing, crusting, and desquamation. With chronic exposure, the skin becomes dry, thick, and scaly with dermal infiltration, lichenification, and fissuring[23].

Table 2 Allergic contact dermatitis distribution and commonly associated sources of exposure[18,23]

Location	Type of exposure
Face/eyelids	Cosmetics, topical medications, or airborne allergens (volatile chemicals, sprays, dust, *etc.*)
Scalp/neck/posterior auricular folds	Hair dyes or shampoos
Sun exposed (face, upper chest, neck, arms)	Phototoxic or photoallergic reaction
Neck/upper chest	Fragrance in perfume or lotions
Hands	Occupational dermatitis (wet work or chemicals)
Trunk and axillary folds	Cloth dyes or textile exposure
Waist band	Rubber component of elastic waistband, nickel from belt buckle or buttons
Dorsal feet	Shoe chemicals (*e.g.*, rubber accelerators, potassium dichromate)

The inflammatory response is typically localized to areas directly in contact with the allergen. However, depending on the allergen sensitivity, the inflammatory response in ACD is well known for its ability to extend beyond areas of direct contact-a feature which distinguishes it from ICD[23]. Additionally, allergens have the potential for secondary transfer, leading to inflammatory presentation beyond the area of initial contact. This is typically seen as "kissing lesions" in flexor regions or areas touched by contaminated hands[23]. While the hands are the most common site for ACD, other common areas include the face, eyelids, lips, upper chest, arms, trunk and axilla, and dorsal feet. Recognizing distribution patterns can be a helpful in understanding ACD exposure (see Table 2 for examples of ACD location and distribution, as well as commonly associated sources of exposure)[18,23].

Histology

Cutaneous changes in ACD can also be observed histologically via light microscopy. Histologic evaluation is important to rule out other conditions that may otherwise clinically resemble contact dermatitis on physical exam. Characteristic findings depend on the severity of response to offending allergens and the time of biopsy after contact with allergen[18,24].

In acute ACD, the epidermis is normal in thickness, and significant inflammatory infiltrates can be observed perivascularly in the dermis[24,25]. Additionally, eosinophilic spongiosis is also a prominent feature - characterized by intercellular edema leading to disruption of intercellular bridging between keratinocytes[24,25]. Fluid accumulation progresses into intra-epidermal vesicles, while dermal perivascular lymphocytic infiltrate and blood capillary dilation result in dermal edema[25,26]. Other common histologic features include, hyperkeratosis, spindled and stellate dermal dendritic fibrohistiocytic cells scattered in the interstitium, and occasional Langerhans cell microgranulomas[24-26].

In sub-acute and chronic cases of ACD, histology is difficult to distinguish from nummular dermatitis or lichen simplex chronicus. Furthermore, while the histologic criteria of ACD occur reliably, they are relatively non-specific and are not readily distinguishable from ICD[18,24]. Sub-acute ACD is characterized by acanthosis and parakeratosis in the superficial cornified layer. Untreated or chronic cases are notable for epithelial ridges that become elongated and broadened. Biopsy is used most commonly for scientific research and is only clinically indicated in patients presenting with atypical symptoms in order to rule out alternative diagnoses (*e.g.,* cutaneous T Cell lymphoma). While histology can aid in diagnosis, current methods do not allow pathologists to readily differentiate ACD from other types of spongiotic dermatitis[27]. Ultimately, diagnosis relies on a combination of history, clinical findings, histology, and positive epicutaneous patch test results[23].

Patch test

Epicutaneous patch testing is the gold standard method for identifying contact allergies[14,28]. Initially a very time consuming process, a majority of patch testing now relies on emulsified gel systems with pre-loaded allergens coated on water impermeable polyester backings. Once applied, allergens are released onto the skin as the dehydrated gel becomes moisturized by transepidermal water. Exposure reactions are then examined at 48 h and re-examined at 72-96 h, directly linking particular contact allergens with hypersensitivity reactions.

Established in 1995, the thin layer rapid use epicutaneous (TRUE) test pioneered this new generation of standardized patch testing. Currently, it remains the only patch test system approved by the Food and Drug Administration. The TRUE test contains a negative control and 35 antigens which includes allergens responsible for up to 80% of clinical allergic contact dermatitis cases[29,30]. The convenience of the TRUE test has allowed for widespread use of diagnostic patch testing in academic centers and private practice dermatology offices. However, with over 4000 known contact allergens, relying on such a limited number of antigens will predictably result in missed diagnoses of ACD[14,29]. Many studies have highlighted this concern, such as Saripalli *et al*[31] who showed that only one quarter of patients would have all clinically relevant allergens identified with the TRUE test, while another quarter would have none identified at all. Similarly, a 2009 study by Warshaw *et al*[32] found that the 36 chamber TRUE test missed 26.7% of contact antigens, particularly common rubber and perfume allergens typically included in an extended 70 antigen panel. Given the TRUE test's restricted diagnostic power,

there is a growing emphasis on more comprehensive screening[19,29,30].

The North American Contact Dermatitis Group (NACDG) was among the first groups to pool ACD data in order to generalize the prevalence of reactivity to allergens in patch tests[7,30]. Based on these results, the most common allergens are selected biennially by consensus for the North American series panel-a larger 70 antigen patch test series[7]. An example of a popular addition to this larger series is fragrance mix Ⅱ (a combination of 6 perfume allergens), which in combination with fragrance mix Ⅰ has been shown to increase fragrance allergy detection by 30% more than fragrance mix Ⅰ alone[33]. Other efforts to raise awareness for contact allergens includes the dubious recognition of "Allergen of the Year," awarded annually by the North American Contact Dermatitis Society to draw attention to common, but under recognized contact allergens. Various dermatology organizations offer alternative patch test series, for example the International Contact Dermatitis Research Group utilizes the widely accepted European Standard patch test series[7]. Other series include the Minimum International Standard, British Baseline, and Japanese Standard.

Logistics and expense prevents including many allergens in a baseline panel. However, supplemental panels should be selected in order to include contact allergens with a higher pre-test probability of being positive according to a given patient's exposure risk (*e.g.,* bakery, dental technicians, hair dressing, metal implants, photochemicals, or metal working, *etc*). Hence, a detailed history is essential for identifying potential allergens. For example, if an allergen in the workplace is suspected, the occupational history needs to include details about the worker's job, their exposures at work, their use of personal protective equipment, work and skin care practices, the relationship of the symptoms to work, and whether other workers are also affected[22]. Examples of specialized series focused on particular industries or jobs include: bakery, dentistry, hairdressing, metal working, and photochemical panels. Examples of specialized series focused on particular chemicals include: acrylates, epoxy, isocyanates, metals, oils and coolants, plastics and glues, and rubber. Specialized trays have been found to have a clear added value, with studies finding 5% of plastics and glue allergies as well as 11% of rubber allergies going undetected by standard screening trays[34,35].

Despite the availability of patch testing and the relative technical ease of administering the test, there are limitations[14,29]. Reading patch test results in particular is dependent on practitioner skill and experience. The NACDG estimates the sensitivity and specificity of patch testing to be both below 85%, with a false positive range of 15%-18%[36]. This confusion often arises during evaluation of weak positive results. Cases of extensive erythema and induration make differentiation between ICD and ACD difficult, particularly in the face of unclear clinical relevance[14]. While ICD tends to decrease by reading at 72 compared to ACD, many cases will not change in appearance, stretching the limits of morphologic interpretation. According to guidelines for interpretation, ICD cannot be definitively ruled out, and ACD cannot be definitively ruled in[14]. In cases with unclear positivity or unclear clinical relevance, alternative tests such as repeated open application test (ROAT) and usage testing should be considered.

The ROAT utilizes one test allergen at a time without occlusion, minimizing rates of ICD and false positive reactions[3,14,37]. It requires the application of 0.1 mL of the test allergen to a pre-specified area (usually the antecubital fossa) twice daily for up to 28 d, or until an eczematous reaction pattern develops[37]. The ROAT allows practitioners to test the clinical relevance of previous patch test results. It is important to note that although a patient might display negative results when the allergen is applied on normal skin, ACD may still manifest during episodes of skin disease or damage[37].

Another alternative for negative or unclear patch test results is usage testing. This involves having the patient use a product with specific ingredients, in order to test sensitivity under real world conditions. This method allows for all factors that may predispose a patient for ACD (friction, damaged or pre-sensitized skin) to be tested[38]. However, this method of testing is limited because it is unable to distinguish an ICD *vs* ACD response. A discussion of proper methodology for patch testing with non-standardized allergens has been reviewed thoroughly by De Groot (2009)[39] Despite these limitations, patch testing remains the most reliable method of diagnosing ACD.

Confocal microscopy

A proposed alternative to patch testing is reflectance confocal microscopy (RCM)[40,41]. RCM is a relatively new non-invasive *in vivo* imaging technique that allows for real-time imaging of the epidermis and superficial dermis[11,40,41]. ACD and ICD are histologically very similar, and are not easily differentiated with traditional histologic methods. However, subtle differences do exist-with deeper, more prominent infiltrate and follicular spongiosis in ACD compared to ICD[11]. These distinctions are deemed less reliable and not histologically definitive given the risk of specimen damage during biopsy collection and the introduction of handling artifacts during fixing and staining[25,26]. In contrast, RCM allows evaluation of cellular and subcellular changes over time with serial observations of affected areas. Astner *et al*[40,41] demonstrated the ability to distinguish ACD from ICD, offering RCM as a promising alternative method of diagnosing ACD.

Once patch testing and clinical history both confirm ACD, measures should be taken to treat symptoms and prevent further exposure.

MANAGEMENT

Successful management of ACD necessitates both prevention and therapy, initially managing symptoms with corticosteroids, while allergen identification and avoidance education are completed[19].

Prevention

ACD prevention relies on allergen avoidance[19]. This requires eliminating exposure to substances clinically suspected and diagnostically confirmed to be causative from the home and work environment. Avoidance of the offending allergen(s) can drastically reduce incidence and severity of ACD[20]. However, even with avoidance, ACD can persist-this is particularly notable in patients with ACD caused by chromate in which less than 20% of cases clear after 10 years[42]. Protective equipment at work should be considered if symptoms or risk of allergen exposure persist. Barrier protection, such as gloves, safety goggles, and respirators, are effective for some workers[20,22]. If occlusive gloves are used regularly they may cause skin irritation. Cotton liners should be recommend to prevent the development of impaired skin barrier function[32].

In addition to barrier equipment, protective creams may also improve skin barrier function. Topical skin protectant (an emulsion with perfluroalkylpolyether) and quaternium 18-bentonite lotion can prevent urushiol-induced dermatitis, while creams containing the chelator diethylenetriaminepentaacetic acid can prevent nickel, chrome, and copper dermatitis[43]. However, in general there is mixed evidence for the effectiveness of pre-work barrier creams[44]. They may be more effective if used in combination with cleansing and after-work creams or emollients. Pre-work barrier creams should not be used by workers who wear latex gloves, because they may increase allergen uptake from gloves[19,43].

Education is an essential part of prevention. Holness *et al*[45] found that workers seldom receive health and safety training related to skin protection. Thus, it is important for practitioners to set aside ample time to counsel patients on allergen avoidance and barrier protection methods. Encouraging patients to read product labels in order to screen for ingredients is an important part of behavior modification. However, practitioners should recognize that ingredient names are complex and may make compliance difficult[19,46,47]. Physicians should consider using free web-based resources (*e.g.,* www.contactderm.org, www.allergyfreeskin.com, or www.mypatchlink.com) that provide patient-friendly education, including detailed lists of products free of patients' particular allergens in order to help improve allergen avoidance and quality of life[19,43,46]. While the efficacy of various forms of education remains unknown, failure to educate patients on how to avoid, or protect against, contact allergens may result in therapy regimens that are ineffective at controlling chronic ACD and episodes of relapse.

Therapy

Topical steroids are the mainstay of ACD symptomatic therapy. The spectrum of potency and ingredients allows the titration of treatment to match the severity and location of the dermatitis. The combination of barrier creams with moderate to high potency steroids have repeatedly been shown to successfully control ACD symptoms[43]. However, long term topical steroid use is often discouraged. In widespread or poorly controlled cases, short term pulse therapy paired with systemic corticosteroids may be considered to bring dermatitis under control rapidly. Additionally, in cases of secondary impetiginization, topical antibiotics (*e.g.,* mupirocin) or oral antibiotics, such as cephalosporin or penicillinase resistant penicillin, are appropriate[43].

Less well studied alternatives treatments include topical calcineurin inhibitors, ultraviolet light therapies (PUVA or UVB), or systemic immune modulating therapies (azathioprine, cyclosporine, methotrexate). Interestingly, since histamine is not a primary inflammatory mediator responsible for pruritus in ACD, anti-histamine treatments are less effective, and are often only prescribed for their sedating side-effects[14].

CONCLUSION

ACD is one of the leading causes of occupational skin diseases and significantly impacts quality of life. The best prognostic indicator for treatment of ACD is early recognition and intervention. Accurate identification of an offending allergen requires a detailed history of potential exposures and a physical examination to confirm the signs of ACD. Patch testing remains the gold standard for diagnosis, but is ultimately limited by the expertise of the clinician and the availability of relevant contact allergens. Management of ACD is multifactorial, relying on both prevention (eliminating allergen exposure, using protective equipment, and educating the patient) and medical therapy (typically topical corticosteroids).

While there continue to be significant improvements in our understanding of ACD, there is still much to be learned, particularly in the arenas of prevention and treatment. Patient education is critical for compliance with ACD prevention strategies. Future ACD management research should focus on the efficacy of various forms of patient education (handouts *vs* online resources *vs* healthcare led seminars, *etc.*). Additionally, ACD treatment is relatively limited to traditional corticosteroid regimens. The field would benefit from large, prospective longitudinal studies of alternative treatment techniques. Regardless of the research focus, studies that evaluate functional outcomes measures, such as time to return to work, would go far to enhance our understanding of the practical effectiveness of current management and treatment methods.

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