Review

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Latex Medical Gloves: Time for a Reappraisal

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Key Words

Gloves · Latex · Natural rubber latex · Synthetic materials · Barrier properties · Allergy · Allergens · Prevalence

Abstract

Many hospitals have implemented policies to restrict or ban the use of devices made of natural rubber latex (NRL) in healthcare as precautionary measures against the perceived risk of NRL allergy. Changes in glove technology, progress in measuring the specific allergenic potential of gloves and a dramatic decrease in the prevalence of NRL allergies after interventions and education prompted us to revisit the basis for justifiable glove selection policies. The published Anglophone literature from 1990 to 2010 was reviewed for original articles and reviews dealing with the barrier and performance properties of NRL and synthetic gloves and the role of glove powder. The review shows that NRL medical gloves, when compared with synthetic gloves, tend to be stronger, more flexible and better accepted by clinicians. The introduction of powder-free gloves has been associated with reductions in protein content and associated allergies. Recently, new methods to quantify clinically relevant NRL allergens have enabled the identification of gloves with low allergenic potential. The use of low-protein, low-allergenic, powder-free gloves is associated with a significant decrease in the prevalence of type I allergic reactions to NRL among healthcare workers. Given the excellent barrier properties and operating characteristics, dramatically reduced incidences of allergic reactions, availability of specific tests for selection of low-allergen gloves, competitive costs and low environmental impact, the use of NRL gloves within the hospital environment warrants reappraisal.

In the 1990s, T.P. participated in the development of FITkit® technology. The kit was launched in 2001. T.P. is the co-chairman of the American Society for Testing and Materials (ASTM) Committee D11, Task Group 40.08 that generated the ASTM D7427-08 Standard [Standard Test Method for the Immunological Measurement of Four Principal Allergenic Proteins (Hev b 1, 3, 5 and 6.02)] in Natural Rubber and Its Products Derived from Latex, published by ASTM in 2008.
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Introduction

In recent years, many hospitals and health care settings around the world have decided to restrict the use or totally ban all natural rubber latex (NRL) devices as precautionary measures to NRL allergy threats. As is widely acknowledged, type I or IgE-mediated NRL allergy has, for several years, been one of the most significant occupational health problems [for reviews, see 1–3]. However, it is now also acknowledged that new cases of NRL allergy have reduced significantly and sometimes virtually disappeared in countries and hospital regions where health authorities have required the use of low-allergen/low-protein, non-powdered protective medical gloves. Thus, policies which ban the use of NRL devices may be an overreaction that can lead to unexpected compromises in the primary purpose of using protective gloves, that is, providing a competent barrier to protect against infections for both healthcare professionals and the patients [4, 5]. These controversies prompted us to revisit the basis for justifiable glove selection policies.

As is well known, NRL has been used as a material for the production of gloves for almost a century. Throughout the 1990s there were increasing concerns about transmittable diseases, particularly HIV infection and hepatitis, which resulted in a dramatic increase in the use of NRL gloves. Escalating glove use in the 1990s was associated with the rise in reports of allergic reactions to NRL gloves among healthcare workers [1, 6–10]. The increased demand for gloves led to an upsurge in glove production, especially in Malaysia. Between 1987 and 1989 the Malaysian Rubber Development Board received over 400 applications to form glove companies where previously only 25 existed [11]. Early on in the history of NRL allergy, some authors [12, 13] suggested that the increased production in response to the sudden upsurge for latex gloves often led to inadequate leaching to reduce protein levels.

The healthcare community requires medical gloves, both for examination and surgery, in order to provide a barrier that prevents transmission of micro-organisms to and from patients [4]. Many factors are involved in the choice of materials for the production of medical gloves, which relate to both the protective effect as well as ease and comfort of use [14, 15]. For a large number of healthcare practitioners, NRL continues to be the glove material of choice [15, 16].

The negative aspect of NRL glove use, linked to the allergy problems, has gained substantial media coverage, in addition to the publication of a significant number of scientific papers. In reaction to the media and scientific coverage, and to rising compensation claims, many hospitals around the world have implemented new latex allergy and glove policies, resulting in the substitution of NRL gloves with synthetic gloves in certain areas, on specific patients or by sensitized staff. More recently, a number of high profile hospitals, exemplified by Johns Hopkins Hospital in Baltimore, Md., USA, and the Cleveland Clinic's network of nine hospitals in Cleveland, Ohio, USA, have gone 'latex free' [5]. As a result, a small but increasing number of medical practitioners only have access to gloves made from synthetic materials. Such policies require full consideration of all of the factors involved, including also glove functionality as well as costs incurred, both directly and indirectly on the environment.

Following recognition of the problem of NRL sensitivity in the late 1980s and early 1990s, many changes were made in the production processes for NRL gloves and in the implementation of latex-sensitivity protocols in hospitals. In recent years, these changes have resulted in a significant reduction in the prevalence rates of allergic reactions to NRL. Experience from the Mayo Clinic, Rochester, Minn., USA [17] and Finland [18] showed that the change by an institute or hospital district specifically to low-allergen gloves or to gloves with undetectable allergen contents, led to a decrease in the incidence of new cases of occupational allergy. In Germany, Allmers et al. [19] showed that a combination of educating physicians and administrators, together with regulations requiring that healthcare facilities only purchase low-protein, powder-free NRL gloves, can even lead to prevention of sensitization.

This review compares the key properties of gloves made of NRL and synthetic source materials and examines glove barrier and functional characteristics, recent changes in glove technology, developments in NRL allergen measurement methodology as well as priority given by clinicians and other health care workers. The Anglophone literature limited largely to the period from 1990 to 2010 was surveyed for original research reports and review articles addressing also specifically the evidence for the consequent reductions in risk of allergic reactions and changes in the epidemiology of NRL allergies.

Glove Source Materials

Many plants produce liquid latex, but the natural material, NRL, used in rubber manufacture is almost exclusively obtained from the *Hevea brasiliensis* tree. It con-

tains the rubber polymer, *cis*-poly-isoprene, as well as varying amounts of a large number of different proteins [20–22]. Various chemicals, such as accelerators, activators, anti-oxidants and vulcanizing agents, are used in the manufacture of medical gloves [23; for review, see 24] but a large proportion of these chemicals are then leached out in the further stages of production, through processes such as 'wet-gel leaching'. These leaching processes also remove the majority of the water-soluble proteins found in NRL [24].

The raw materials for synthetic glove manufacture include vinyl (polyvinyl chloride), nitrile (acetonitrile butadiene), neoprene, polyisoprene, polychloroprene, polyurethane and polyethylene, which are generally derived from oil chemistry. Nitrile is very similar in its polymer chemical structure to NRL and, in this respect, may be considered as synthetic latex.

Deproteinised latex, being composed of enzyme-treated NRL, has also been used as the source material for gloves [25]. We are not aware of published reports in which gloves made of deproteinised NRL have been compared with conventional NRL gloves, especially with respect to their allergenic properties, although there are reports that NRL-allergic patients can tolerate condoms made from this material [26].

Recently, liquid latex from a North American and Mexican desert shrub, *Parthenium argentatum,* commonly known as Guayule, has been introduced as source material for gloves [27]. The obvious advantage of Guayule is that it is not botanically related to *H. brasiliensis* and, for the time being, no reports about type I allergies to these gloves have been reported.

Glove Properties

Barrier Properties

The primary function of gloves is to provide a competent barrier to protect against infections for both healthcare professionals and the patients. Gloves used by healthcare workers need to be single use for each patient contact and treatment, although it is recommended that prolonged and indiscriminate use should be avoided to minimize the risk of sensitization [4]. They are required in various situations such as invasive procedures and contact with non-intact skin, mucous membranes or sterile sites. As such, leakage must be minimal, even when apparently undamaged, and various standards have been developed in order that all gloves perform adequately regardless of material [4]. They should be easy to put on, comfortable to wear and provide adequate, durable protection [15].

The durability of barrier protection has been examined in a number of studies and it has been shown that NRL gloves provide lower rates of perforation and lower viral leakage rates than vinyl gloves [24, 28, 29]. In a study that examined gloves after manipulation to simulate in-use conditions, the failure rate was 0–4% for NRL, 1–3% for nitrile and 12–61% for vinyl gloves, indicating better barrier protection by NRL and nitrile gloves, compared to vinyl [29]. In another study where gloves were stressed according to a designated protocol before examining for leakage properties, failure rates were 2.2% for NRL and 1.3% for nitrile gloves, which were again better than for vinyl or copolymer (8.2% for each) [30]. Barrier integrity following an abrasion test demonstrated that NRL gloves were better than vinyl, although not as good as either nitrile or neoprene [31].

A study in the USA in 2004 performed post-usage examination and testing of surgeons' gloves after routine surgical procedures. The results revealed higher after-use defects for non-latex compared with latex gloves [32]. Compared with NRL gloves, the odds ratio for defects was 1.39 (95% confidence interval 1.12–1.73) for neoprene and 1.90 (95% confidence interval 1.15–3.13) for nitrile gloves. In addition, the surgeons reported significantly greater satisfaction with regard to factors such as quality, safety and durability for latex compared with non-latex gloves. These results should probably be treated with caution because the surgeons had never used non-latex gloves before for routine surgery (acknowledged by the authors as a possible bias) and only 215 nitrile gloves were used compared to 2,647 latex and 3,624 neoprene gloves. In addition, the main difference in the study was in visible leaks, with no significant difference in water leaks, which may be explained by the low tear propagation strength of nitrile/neoprene. Similar differences between neoprene and NRL have been demonstrated in another study [33] where it was noted that punctures in neoprene gloves were detected more readily by surgeons than punctures in NRL gloves.

A recent study [34], comparing synthetic polyisoprene and NRL gloves during heavy orthopaedic surgery with high risk of perforations, revealed a significantly higher perforation rate in latex-free gloves (80.0%) compared with NRL gloves (34.4%). Again, the study was poorly controlled and open to criticism because glove usage was not randomized, being based on two surgical teams in two different hospitals, one using NRL, the other using polyisoprene. It is, however, interesting that these three

studies appear to detect highly significant differences in perforation rates between NRL and non-NRL [32–34].

Fit and Comfort

According to the Scientific Committee on Medicinal Products and Medical Devices of the European Commission [35], nitrile gloves are usually of lower tensile strength than latex gloves, but their elastic modulus, or stiffness, is somewhat higher. In addition, nitrile has a higher permanent set than latex, meaning that once stretched it does not fully recover. Thus, nitrile gloves tend to be designed to fit more loosely than latex, and the combination of these properties may affect the users' tactile sensation and delicacy of touch. This has been confirmed by a study [36] where participants noted that nitrile gloves that fitted their fingers were too narrow for their hands and gloves that fitted their hands were too large for their fingers. During this research, it was confirmed that there are detectable differences between nitrile and latex, where a pegboard test demonstrated an 8.6% increase in fine finger dexterity for latex over nitrile, although no differences related to gross dexterity. Whilst it is not clear at present what the practical effects of this research mean, it does appear that the stiffness of nitrile may affect user dexterity. The study also questioned users about their preferred material, with 67% preferring latex and 21% preferring nitrile.

Thus, a variety of factors, including glove strength, abrasive resistivity, dexterity and comfort, should be taken into account when selecting gloves for specific needs.

Enhanced Barrier Performance by Means of Double Gloving

When carrying out operations, perforations in gloves often go unnoticed and there is frequently a risk of contamination and exposure to blood-borne pathogens [37, 38].

As a result, double gloving has been routinely used by a proportion of surgeons since the early 1990s. However, double gloving is reported to be less common in the UK, Europe and the USA than in other countries, except in the areas of orthopaedics and maxillofacial surgery [38, 39]. Double gloving is generally carried out with two layers of NRL gloves [38], although sometimes the inner glove can be synthetic, which may reduce the risk of allergic reactions.

One study found that double gloving was able to prevent contamination by needle-stick injuries from cutting suture needles, although single-layer gloves were just as good as double gloves for tapered suture needles [40]. Caution should be exercised in extending these data to clinical practice because the test solution was water, which is dissimilar in viscosity to blood. Nevertheless, an analysis of a number of published trials showed that there were significantly more perforations to single gloves than to the inner glove of double gloves [38]. The failure rate from blood contamination of the fingers in one study of surgeons was significantly decreased from 13 to 2% ($p < 0.005$) [37]. Another similar study among surgeons reported blood contamination to be 51% with single gloves and 7% with double gloves [41]. This particular trial also reported that 88% of the surgeons who tested double gloving found the technique acceptable. Some studies have shown that loss of dexterity is often cited as a reason for not using double gloving [38, 39] and others have shown a general tendency for surgeons to dislike double gloving [42].

A recent review of gloves used in surgical operations concluded that while a basic level of protection for low-risk surgery can be achieved by single gloving, double gloving provided significantly higher levels of protection against perforations typically acquired in medium-risk surgery. The highest level of protection required during high-risk surgery, such as orthopaedic and maxillofacial operations as well as cardiac surgery, was provided by glove liners, knitted gloves and triple gloving [43]. The author further recommended that when neither the patient nor the operating personnel are allergic to NRL, high-quality low-allergen NRL gloves should be used at all these levels to ensure the best available barrier performance.

Adverse Reactions

Adverse reactions to medical gloves can be characterized into three main types: irritant contact dermatitis, type I allergic reactions and type IV allergic reactions [14]. The distinction is, however, relevant from the glove users' point of view because irritant contact dermatitis is the most common reaction but is not mediated by the immune system and, therefore, can occur with gloves made from any material. It typically involves dry, crusted lesions, localized to the glove-exposed areas on hands and wrists.

A type I reaction is a true immune-mediated response involving prior IgE production following exposure to allergenic proteins or polypeptides that occur in latex products [14, 21, 44; for review, see 45]. It most frequently presents as cutaneous reactions, typically as contact urticaria,

although it may involve other organs, such as the eyes and lungs, resulting in rhinoconjunctivitis and asthma, and can be life threatening if anaphylaxis occurs [46].

Type IV reactions, known as delayed-type hypersensitivity, are typically present as allergic contact dermatitis and occur in response to chemicals present in gloves, generally as a result of the manufacturing process. Such chemicals include, in particular, accelerators such as thiurams, carbamates, thiazoles, thioureas and guanidines. A type IV reaction can also be induced by other chemicals, including those in perfumes, lotions and cleaning materials applied prior to glove use, and may be an increasing problem with stricter hospital hand-cleaning policies due to resistant bacteria. For instance, the current trend of using alcohol hand rubs may exacerbate type IV reactions, perhaps by unevaporated solvent on the hand acting as an efficient extracting agent for residual glove chemicals. A recent evaluation of pre-operative surgical hand rubs [23, 47] reported a case of mild to severe irritant dermatitis related to donning gloves before all the alcohol had dried.

Decreasing Incidence and Prevalence of Type I Allergy

Healthcare Workers

At the end of the 1990s, NRL allergy was reported to have reached epidemic proportions and to be a significant medical concern [48, 49]. Correct diagnosis of type I latex allergy requires a thorough clinical history of exposure to latex products, positive skin prick tests and/or positive specific IgE blood tests, such as the latex radioallergosorbent test. Studies of healthcare workers based on skin prick testing have generally reported the prevalence in the 1990s to be around 3–12% [for review, see 50].

At the time of peak reporting, there were large variations in estimates of prevalence of NRL allergy among healthcare workers between different studies. High prevalence rates were often seen if the assessment was based primarily on serum IgE measurements and not on skin prick testing. Studies usually showed a relationship with exposure, although, interestingly, prevalence of type I allergy was often only around 1.5% among workers producing the latex and the gloves [51, 52]. A recent international meta-analysis comparing the prevalence of NRL allergy in healthcare workers and in the general population, extending until 2003, found NRL allergy in 4.3% of healthcare workers and in 1.4% of the general population [2]. The authors, however, pointed out that the results should be viewed with caution because the methods used in skin prick tests and serum IgE measurements vary and the results under such circumstances are not consistent. Moreover, because studies from the USA have consistently reported higher prevalence rates, this meta-analysis almost certainly over-estimates the actual prevalence rates within most of Europe.

Experience from the Mayo Clinic [17], emphasizing the importance of quantitative latex allergen measurement, showed that the change by the institute to low-allergen or undetectable allergen gloves led to a reduced concentration of allergens in the work place and decreased the number of new cases of occupational allergy. In addition, over the last decade there have been strict policies of using low-protein or low-allergen, powder-free NRL gloves in many hospitals and in some countries, particularly Finland, Germany, Italy and the UK. Recent German and Italian studies show that education about NRL allergy, combined with the use of powder-free NRL gloves with reduced protein levels, has caused a steady decline in the numbers of sensitized healthcare workers [19, 53, 54]. The use of glove powder was effectively regulated by national laws in Germany and Switzerland (ratified in 1998) where the use of powdered latex gloves by healthcare workers was explicitly banned; German law states that 'latex gloves have to be powder-free and low in allergens'. This has apparently influenced the development of new cases of sensitization and has enabled a large reduction in the reported incidence of type I allergic reactions [2, 17, 19, 53, 55]. At the same time the American Academy of Dermatology's position paper on latex allergy states in their recommendations that 'all medical and dental facilities are encouraged to exclusively use powder-free gloves with low NRL allergen levels' [14].

LaMontagne et al. [56] noted in their systematic review of eight primary prevention intervention studies that substitution of powdered latex gloves with low-protein, powder-free NRL gloves or latex-free gloves greatly reduced NRL aeroallergens, NRL sensitization and NRL asthma in healthcare workers. Furthermore, the recent article by Vandenplas et al. [57] clearly shows how the decreasing use of powdered NRL gloves in healthcare in Belgium was associated with a sharply decreasing incidence of latex-induced asthma, evidenced by national compensation-based data. Of interest is the replacement of powdered NRL in Belgium mainly by synthetic gloves for non-sterile procedures. The actual prevalence of type I latex allergy in healthcare workers has been reported to be less than 1% in hospitals with strict NRL policies [18, 54, 55, 57–59] particularly in Europe.

Importantly, several studies show that healthcare workers or other patients with diagnosed NRL allergy have been able to continue their work in hospitals and healthcare settings where low-allergen, low-protein and usually powder-free gloves have been used [17, 18, 55, 57, 60–63]. As summarised by Hunt et al. [17], these studies generally demonstrate that NRL-allergic healthcare workers who, despite the need to use non-latex alternatives for their personal use, can continue to work in their medical environment if they use either non-powdered latex gloves, latex gloves of lowest protein content or latex gloves of very low allergen content. With these modifications, symptoms from aeroallergen exposure are prevented and new cases of latex allergy are reduced. In one of these studies [18], a large cohort, that is, the entire healthcare sector of a large Finnish university hospital comprising of 160 latex-allergic healthcare workers, has changed to low-allergen gloves. On re-examination at a median of 3 (0.5–11) years, none of the healthcare workers had changed work because of NRL allergy. Interestingly, the majority of latex-allergic healthcare workers continued to use low-allergen latex gloves.

General Population

Relatively few studies have been carried out to examine the prevalence of NRL allergy in the general population. The results from control groups examined by skin prick testing have indicated the prevalence of type I NRL allergy in Western Europe to be approximately 1% or less [2, 18, 22, 49, 50]. These data would suggest that in Europe, although perhaps not in the USA, the reported prevalence among healthcare workers is now very similar to that for the general population.

Atopic individuals generally have higher prevalence rates [22, 48, 50, 64, 65] and there are known cross-reactive allergic reactions. Individuals who are allergic to certain fruits, such as kiwi fruit, bananas, chestnuts and avocados, are frequently allergic to NRL as well [7, 64, 66–69].

The prevalence in certain groups of people can be much higher. In particular, prevalence rates in individuals who have received multiple operations involving exposure to NRL-containing materials, at an early age, such as patients with spina bifida, short bowel syndrome or urogenital abnormalities [18, 70, 71], have been reported in the earlier studies to be up to 60%, although this also appears to be decreasing due to reduced exposure to NRL [72].

Therefore, questioning patients with regard to specific allergies and medical history may identify those who are likely to have a (possibly undiagnosed) type I allergy to NRL [73]. Screening of patients is often undertaken by anaesthetists and backed up by further questioning by theatre nursing staff. This can enable appropriate measures to be taken to avoid allergic reactions, and many hospitals now have latex-free operating theatres or access to latex-free equipment that can be deployed when necessary.

The Role of Glove Powder

The surface of NRL gloves, naturally, has a strong adherent grip when untreated. Surgical gloves were originally boiled and donned when wet [74]. When dry sterilization was introduced, various powders were used as a lubricant to aid donning of the glove. Originally, talc was used, but it was found to be associated with granulomas and adhesions [75]. In the 1940s, modified cornstarch powder was introduced into general use because it was believed to be a safe alternative. Unfortunately, it also was demonstrated to be responsible for adhesions and granulomas, probably due to a move from autoclaving to γ-irradiation [74]. In the 1990s, when allergic reactions became recognized as a problem, it was shown that the modified cornstarch could act as a vector for the allergenic proteins, which bound to the cornstarch and were thereby transferred from the NRL gloves to staff and patients [76, 77]. Not only can the powder carry the proteins into wounds, but it can become airborne and act as a carrier for antigens from the gloves [78]; powdered gloves have been shown to increase airborne NRL antigens compared with non-powdered gloves [79].

As a result of these concerns, powder-free gloves rapidly became available and have become accepted into general use. Powdered gloves are still available for certain applications within the healthcare and hospital environment, for example where their superior grip properties are particularly useful, but their use is generally restricted to areas where the risk of powder contamination is low. The quantity and nature of the powder and the definition of powdered versus non-powdered gloves is carefully regulated by materials testing agencies [80]; for the purpose of the European Standard (EN 455), a powder is defined as all water-insoluble material on the surface of a glove that is removed by washing under the conditions of the test, and any glove containing more than 2 mg of powder is classed as a powdered glove, whilst gloves with 2 mg or less powder are classed as powder-free. The American Society for Testing and Materials (ASTM) D3577-06 and D3578-06 standards for surgical and examination gloves, respectively, also have a maximum powder limit of 2 mg/glove.

Changes in Glove Manufacture Processes

The processes used for NRL glove manufacture have changed greatly in recent years. One of the major changes was the switch to chlorinated powder-free gloves: while removal of powder may have eliminated the possible transport of allergens, the concomitant lower allergenic potential may be coincidental. Chlorination usually involves a number of different processes, including acid neutralization and a number of leaching steps. It has been shown [81] that the processes associated with chlorination (neutralization, washing with water) are almost equally as effective on their own without free chlorine, resulting in effective leaching of the proteins [25]. The addition of a chlorination process during manufacture has been associated with lower levels of extractable proteins (EP). However, the leaching processes and finishing treatments necessary to remove residual chlorine and other chemicals appear to be responsible for the major reduction of allergenic protein levels. In line with this, Yip et al. [13] demonstrated that non-chlorinated gloves which underwent a 5-min wet-gel leaching followed by a 5-min dry-film leaching process did not produce skin prick testing allergic responses in patients with known latex hypersensitivity. Chlorinated gloves in the same study had a lower level of EP, but initiated a weak positive reaction in 27% of these patients. Similarly, Dalrymple and Audley [81], when examining the effects of various treatments on EP levels in an exhaustive set of experiments, stated that whilst 'chlorinated products are characteristically low in EP this appears to result from exposure to the water, salt, acid and ammonia associated with the process, and not from chlorination itself'.

Time and temperature of storage of NRL appear to be important; during transport, where high natural temperatures may be encountered, there was actually a drop in allergic potential due to degradation of some proteins [82], and ageing of the NRL product also appears to reduce the allergic potential. The modern NRL glove manufacturing processes, with on-line leaching and high temperature, post-washing procedures, have resulted in gloves with much lower allergenic potential and have had a clear impact on the low incidence of type I allergy currently reported.

Glove Purchasing Policies

It is also likely that the purchasing patterns for gloves in different countries explain the widely varying rates of type I allergy described in the literature. In Finland, the National Agency of Medicines has, since 1994, carried out bi-annual market surveillances on all medical gloves on the Finnish market. The studies have made use of a human IgE enzyme-linked immunosorbent assay (ELISA) inhibition test [83] and also, since 2003, a commercial capture enzyme immunoassay for four principal latex allergenic proteins [84]. The results have been categorized according to the content of allergens to low, medium and high levels, and published on the website of the National Agency of Medicines (www.nam.fi/english/publications). Many Finnish hospitals have been using these reports as their basis for glove purchasing policies and, apparently, numerous institutions in other countries have been taking advantage of this information as well. No new occupational type I latex allergies have been reported in the last 5 years in the Finnish Occupational Skin Disease Registry [Alanko, pers. commun., 2009].

Given the low prevalence rates of NRL allergy among healthcare workers in the UK [52, 58, 59], it is interesting to note that during the early 1990s, when it is believed that protein levels in gloves peaked globally, most UK hospitals were continuing to buy from a small number of experienced and reputable manufacturers. In retrospect, it is difficult to know what levels of allergenic proteins were present in all brands of gloves over this period, but if the experienced manufacturers continued to use extended leaching to remove residual accelerators and other chemicals, low protein levels and thereby low allergen levels would have been a by-product of this process.

Evidence from one of the author's laboratories shows that in 1996, powdered NRL examination gloves from one of the main UK suppliers had low levels of EP (29 μg/g) compared to the other powdered gloves on the market (median 153 μg/g, range 88–512 μg/g). During the early 1990s, many UK hospitals continued to use predominantly a particular brand of examination glove of which there were test data showing that they had low levels of pinholes when tested using the (at the time) proposed EN 455 water test. Whilst regular protein testing was uncommon at this time, the 1996 data indicates that the act of purchasing gloves based on their pinhole levels may have serendipitously led to the use of gloves also low in EP. Thus, the purchasing patterns from more than a decade ago may account for the differing levels of sensitization that have been reported.

Subsequently, the UK, in line with most European countries, started purchasing powder-free gloves in the 1990s, and continued to use powder-free, low-protein gloves within the National Health Service. A recent guideline on managing latex allergy from the UK Royal

College of Physicians [3] stated that 'no reports of new cases of latex allergy arising from non-powdered low protein latex glove use were found'.

Prevalence of Type IV Allergy

In addition to type I allergies to NRL proteins, there may be type IV allergies to chemicals used in the manufacturing process, such as various accelerators of vulcanization and antioxidants. Type IV reactions are generally considered more common than type I reactions and a high prevalence rate of type IV allergy among healthcare workers has been highlighted in several surveys [3, 23, 85, 86]. Skin patch testing using NRL glove extracts can demonstrate a response to both specific protein allergens and the chemicals present and so will be a combination of both type I and IV reactions. In a study carried out in Italy, 1,294 healthcare workers who used NRL gloves were questioned and 316 reported skin symptoms associated with glove use [23]. Among those with skin symptoms, 27 had a type I allergic reaction to NRL and 31 had a type IV reaction, identified by skin patch tests to a series of rubber additives. In a prospective study of 2,738 patients, the overall prevalence of type IV reaction to NRL was found to be 1% [87]. Similar to type I allergy, the prevalence in these patients was higher for those reported to be atopic and who had eczema on the hands.

There do not appear to have been any studies that have reported the change in incidence of type IV reactions over time. However, similar to the effect that the enhanced leaching had on reducing type I allergies, it would seem reasonable to deduce that there has also been a reduction in residual chemical levels that can cause type IV reactions. Thus, it is likely that type IV prevalence associated with powder-free NRL has declined in recent years due to lower residual chemical levels [88].

Most synthetic gloves also require the use of accelerators during manufacture. It has been hypothesized that because there is no chlorination process, leaching times may be shorter than for NRL and, therefore, some synthetic gloves may exhibit higher residual levels of chemicals than NRL, which are sufficient to induce type IV reactions [89]. Lauren et al. [90] report apparent increases in skin allergies associated with a switch to synthetic gloves, probably associated with accelerators, as well as a reduction in choice of synthetic alternatives. Some manufacturers are now producing synthetic gloves (mainly nitrile) which no longer contain accelerators.

It should also be noted that some NRL gloves use casein as a binding agent in the jellification of latex. Allergic reactions to gloves containing casein have been noted and so these gloves should be avoided to reduce the risk of allergic reactions [91, 92].

Allergenic Potential of NRL Gloves

The allergenic potential of gloves has, in some studies, been indirectly estimated according to the total protein content measured by the modified Lowry test [93, 94]. The method is standardized by the US (ASTM) and European (Committee for Standardization, CEN) standardization authorities, but this is a non-specific determination that will detect, in principle, any protein, not just IgE-binding allergens. Moreover, it is susceptible to accelerators and surfactants used in the NRL manufacturing process, which can either enhance or suppress the reported protein levels. It has also been suggested that it is not sensitive enough in the low protein range [95]. The ASTM method and the Lowry method modified by the CEN have, however, been widely accepted over the last decade since there was reasonable correlation between total EP and skin prick tests. The opinion of the Scientific Committee on Medical Products and Medical Devices in 2000 was that a relationship between leachable protein levels and the risk of allergic reaction or sensitization has been demonstrated [35]. ASTM standards for medical gloves (ASTM D3577 for surgical gloves and D3578 for examination gloves) contain recommended limits for aqueous EP to be less than 200 $\mu g/dm^2$ (corresponding approximately to 50 $\mu g/g$), but the US government has not defined the term 'low protein', the use of which is thereby not allowed. Protein claims on glove packaging is not mandatory.

The European (CEN) standard EN 455-3 (medical gloves for single use – part 3: requirements and testing for biological evaluation) states that 'the leachable protein level shall be as low as reasonably practicable (ALARP)'. Thus, no definite acceptable limit has been defined.

More recently, specific allergenic proteins present in NRL gloves have been identified using techniques such as two-dimensional electrophoresis, IgE immunoblotting and micro-sequencing [20]. Many of these antigens belong to the group of 13 *H. brasiliensis* proteins currently recognized by the World Health Organization/International Union of Immunological Societies Allergen Nomenclature Committee [45], and sequence homologies for many of these proteins have been shown with proteins

from various fruits or vegetables, offering at least a partial explanation for the cross-reactivity [96].

The major proteins detectable in NRL gloves that have been shown to cause type I allergy among healthcare workers include Hev b 1, Hev b 3, Hev b 5 and Hev b 6.02 [84, 97]. However, in latex-allergic patients, such as those with spina bifida, the major allergens are often slightly different, comprising predominantly Hev b 1, Hev b 3 and Hev b 7, which has been suggested to be partly due to differences in the levels of each protein between the inside and the outside of NRL gloves [98, 99]. This scenario, however, remains to be confirmed in other studies. There is some evidence that Hev b 2 and Hev b 13 may also be significant allergens that can be identified in NRL gloves, although differences in sensitization between geographical regions have been identified and require further investigation [100].

Recent Developments in Measuring Allergenic Potential in Medical Gloves

Using a commercially available capture immunoassay (FITkit® test, Quattromed AS, currently Icosagen AS, Tartu, Estonia), the major allergenic *Hevea* proteins Hev b 1, Hev b 3, Hev b 5 and Hev b 6.02 were recently quantified in 208 NRL gloves marketed in Finland [84] and compared with an IgE-ELISA inhibition test previously validated by skin prick testing in latex-allergic patients [83]. The sum of the concentrations of the four allergens provided a strong correlation with the IgE-ELISA (fig. 1) [84]. Various cut-off values for the sum of concentrations were examined for specificity and sensitivity. It was established that gloves with a sum concentration below a cut-off of 0.15 μg/g could be considered as having low allergenic potential [84]. The initial results from testing had earlier indicated good correlation with human IgE-based methods for measuring allergenic potential [97, 101].

This commercial capture immunoassay fulfils the requirements of the immunoenzymetric assay for the measurement of four allergens that were recently (August 2008) adopted by the ASTM (standard D 7427-08). Whilst the test only evaluates the four *Hevea* proteins considered most clinically relevant and does not identify other potentially unknown antigens, the good correlation with human IgE-based methods suggests that these proteins, especially Hev b 6.02, are significant in determining the allergenicity of NRL gloves. It has not yet been thoroughly assessed whether additional allergens would add significantly to the performance of the assay [102].

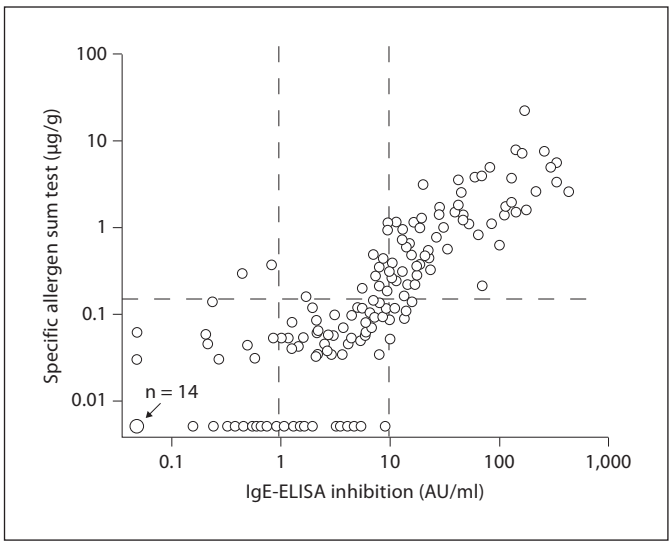

Fig. 1. Relationship between the results from the four-NRL allergen sum test (μg/g) and human IgE-ELISA inhibition test (AU/ml) in 208 medical gloves. In the human IgE-based assay values below 1 AU/ml are considered as 'very low' allergenic, values from 1.0 to 9.9 AU/ml as 'low allergenic', values from 10.0 to 99 AU/ml as 'moderately allergenic', >100 AU/ml as 'highly allergenic'. The vertical dotted lines denote limits for the very low (1 AU/ml) and low (10 AU/ml) limits. The horizontal dotted line marks the 0.15 μg/g limit in the four-allergen sum test. AU = Allergen unit. Reproduced from Palosuo et al. [84]. Copyright 2007 by John Wiley and Sons. Reprinted by permission of John Wiley and Sons via the Copyright Clearance Center's Rightslink service.

Diagnostic Tests in Assaying Sensitization, Clinical Allergy and Prevalence

Reliable diagnostic procedures are required not only to correctly diagnose patient diseases but also to gain comparable prevalence rates in different parts of the world. A number of serological tests to identify latex-specific IgE antibodies have been developed and used to diagnose NRL allergy, and several have also been commercialized [103–105]. However, despite the common use of serum IgE tests, none have been widely accepted into general use and new IgE tests are still being developed to eliminate discordant results and the large number of both false positives and false negatives [22, 69, 103–106]. The recent report of Ebo et al. [107] using component-resolved diagnosis by microarray may provide help in the discrimination of genuine NRL allergy from asymptomatic sensitization, a well-recognized problem in the diagnostics of NRL allergy.

Although type I immune reactions are mediated through IgE antibodies, the presence of IgE reactive with NRL antigens cannot always be assumed to be due to

NRL sensitization because of cross-reactivity that may not have any clinical relevance. Therefore, the gold standard for defining type I NRL allergy and distinguishing it from, for example, irritant (non-specific) and allergic (type IV) contact dermatitis, is considered to be skin prick testing using either NRL extracts or preparations of *Hevea* proteins [104, 106, 108–110]. Unfortunately, no specific procedure for skin prick testing has been universally accepted; *Hevea* protein preparations may not have the most appropriate mix and commercially produced extracts can differ markedly from in-house preparations [55, 106], for example, they may be ammoniated or non-ammoniated giving quite different results [111]. In doubtful cases an adequately controlled use or challenge test (exposure) with a well-characterized high-allergen glove is required for confirming the diagnosis [112].

Relative Economic and Environmental Costs

Natural rubber and rubber products are biodegradable through a combination of chemical and biological attacks, and a number of micro-organisms are able to degrade NRL gloves [24, 113, 114]. Furthermore, many of the alternatives to NRL can produce toxic emissions when incinerated [115].

In contrast to NRL, the raw materials for synthetic gloves are mainly derived from oil chemistry and these materials are not a renewable source. In the production process for the raw materials, it has been estimated that it requires only 16 GJ/ton in the case of NRL, but energy consumption ranges from 108 to 174 GJ/ton for the synthetic materials [116]. The economic costs for the raw materials for synthetic gloves are generally considered to be much greater than for NRL [4].

Finally, conversion from powdered gloves to low-protein, non-powdered gloves was reported to have produced substantial savings when compensation claims were included [117].

Conclusions

With the reduced incidence of allergic reactions, the availability of specific and sensitive testing for the selection of low-allergen gloves, competitive costs and lower environmental impact, NRL remains an excellent choice of material for medical gloves and should continue to be used.

In recent years, a number of high profile institutions have moved to a totally NRL-free environment, including gloves. However, the evidence within Europe demonstrates that the many benefits of NRL can be retained by purchasing low-allergen, low-protein and powder-free gloves, thereby reducing the risk of type I and type IV sensitization as well as allergic reactions. NRL gloves are characterized by a high level of barrier performance for staff and patients, good comfort allowing staff to perform safely and efficiently, and competitive pricing in a period of economic difficulty. NRL is an environmentally sustainable material, which is also naturally biodegradable, enabling hospitals to meet their 'green' purchasing requirements. Finally, compared with various synthetic materials, NRL is generally better accepted by the clinicians. There will, of course, be a continuing requirement for synthetic gloves for known latex-allergic patients and staff, and for these purposes several options are currently available. In conclusion, we believe that a sensible balance requires a mix of latex and synthetic gloves.

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