Adjuvant treatments for recurrent respiratory papillomatosis: a descriptive review and

proposed management guideline in adults

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Abstract

Objective

Recurrent respiratory papillomatosis (RRP) is a rare disease characterised by growth of papilloma within the respiratory tract. The disease course is variable but can require frequent surgical interventions alongside adjuvant medical treatments. There is no definitive curative treatment or gold-standard guidelines for management. We aimed to evaluate current and potential future adjuvant treatments and propose a management guideline for adult patients.

Methods

Relevant articles were identified through searching databases, reference lists, and the grey literature.

Results

Systemic Bevacizumab appears to be the most effective adjuvant treatment currently available. However, intralesional Cidofovir also achieves a high complete response rate in adults and the Gardasil vaccine demonstrates preventative and therapeutic value. The INO-3107 DNA vaccine is a promising potential future adjuvant treatment.

Conclusions

This review provides a detailed examination of current and potential future adjuvant treatments. Based on the literature, we have developed a management guideline for adult patients with RRP.

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Laser

Dysphonia

Trachea

Papillomatosis

Introduction

Recurrent respiratory papillomatosis (RRP) is a rare chronic disease caused by the human papillomavirus (HPV) that is characterised by the growth of benign papilloma within the respiratory tract. The disease is classified as adult-onset (AO-RRP) or juvenile-onset (JO-RRP) based on the age at diagnosis and demonstrates a trimodal distribution with peaks at ages 7, 35 and 64 years[1]. AO-RRP has a male predilection and typically affects individuals between the second and fourth decades of life, with an incidence rate of 1.8 per 100,000 adults. JO-RRP is the most common benign laryngeal tumour in children, with an incidence rate of 4.5 per 100,000[2].

In adults, RRP can manifest with symptoms of hoarseness, dyspnoea, stridor, cough, and recurrent respiratory infections. Paediatric presentation varies based on whether the disease affects the supraglottis, glottis, or subglottis, with early presentation with dysphonia if the glottis is involved. Standardised systems of objective scoring of RRP, such as the Derkay Severity Score, have been developed that allow for assessment of the disease course over time and evaluation of the response to treatment[3]. The Derkay Severity Score combines a subjective clinical assessment with an anatomical assessment of the sites involved and has been shown to positively correlate with voice-related quality of life scores on the Voice Handicap Index-10[4].

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The disease course is variable but can require lifelong treatment with multiple surgeries alongside adjuvant medical treatments to achieve control. While an increasing number of adjuvant treatments have become available over the past two decades, there is currently no definitive curative treatment for RRP or gold-standard guidelines for the management of this condition.

In this review, we aimed to evaluate the current and potential future adjuvant treatment options for the management of RRP. We consider the efficacy and potential side effects of each option and propose a management guideline for adult patients with RRP based on the current literature. Additionally, we evaluate the approach to surgical management of RRP and consider the burden of surgical interventions from both an economic and quality of life perspective.

Methods

Electronic database searches of Embase (1974 – 2023) and Ovid MEDLINE (1946 – 2023) were systematically performed with the following keywords and Meshterms: "recurrent respiratory papillomatosis", "laryngeal papillomatosis", "juvenile-onset recurrent respiratory papillomatosis", "adult-onset recurrent respiratory papillomatosis", "adjuvant treatment", "adjuvant therapy", "quality of life", and "economic burden". The full search can be requested from the corresponding author. The results were screened to identify articles relevant to the creation of the management guideline. Eligibility criteria included articles involving humans, available in the English language, and with the full text available for retrieval. The database search identified 3352 articles with 1273 screened after removal of duplicates and those marked ineligible by automation tools (Figure 1). A total of 1171 articles were excluded after screening and 102 were retrieved and assessed for eligibility, with 16 deemed relevant for inclusion in the development of the management guideline. The main details of these articles are shown in Table 1. The reference lists of included articles were then screened for

additional sources, and grey literature was searched as well. The data and discussions were interpreted and synthesised to create a concise review of the surgical management and adjuvant treatments available for RRP. Based on the findings of the review, we have developed a proposed management guideline for the treatment of adult patients with RRP within the United Kingdom National Health Service (NHS) setting.

Results

Pathophysiology

The HPV virus infiltrates basal epithelial cells of the squamous epithelium through microtears in the overlying cell layers, activating the epidermal growth factor pathway and suppressing tumour-suppressor proteins[5]. Specifically, the proteins encoded by the E6 and E7 regions of the HPV viral genome interfere with tumour suppressor proteins p53 and pRB respectively[6]. This results in cellular proliferation and epithelial differentiation that culminates in the development of papillomatous lesions that can be microscopic or macroscopic and exophytic. These lesions are typically benign, but depending on the specific subtype of HPV involved, they can have varying degrees of malignant potential. In RRP these papillomata predominantly manifest at the junction between the stratified squamous epithelium in the larynx and the pseudostratified columnar epithelium of the respiratory tract distally[5].

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HPV infection is ubiquitous in the population. It is estimated that by 50 years old, 80% of women in the United States have serological evidence of previous infection[7]. While in the majority of cases the virus is cleared by a host cell-mediated immune response, it is estimated that 5% of the general population has HPV DNA detectable in their larynx suggesting persistent infection[8]. It is unclear why a small number of these individuals go on to develop RRP, but it is thought to be related to an ineffective immune response to the viral proteins. While the mechanism is unknown, there is evidence that the adaptive immune response becomes polarised toward a Th2-like or T-regulatory phenotype in these patients. This results in suppression of Th1 cells that would produce the inflammatory cytokines, such as interleukin-2 and tumour necrosis factor, responsible for clearing viral infections[9].

RRP is predominantly associated with HPV sub-types 6 and 11, but can also be caused by other strains, including 16, 18, 31, and 33. Traditionally, HPV 11 has been linked to more severe RRP disease[10]. However, emerging evidence suggests that age at diagnosis may be a more consistent predictor of disease severity, with the probability of an aggressive disease course being higher in patients diagnosed under five years of age[11, 12].

JO-RRP is typically thought to be due to transmission of maternal HPV infection to the child at birth. Trans-placental transmission of HPV has been suggested to occur in 12% of cases[13] and the presence of maternal anogenital papilloma increases the risk of developing JO-RRP by 231 times[14]. First-born status, vaginal delivery, and being born to a teenage mother have also been reported to increase the risk of JO-RRP[15]. AO-RRP has historically been thought to potentially be a sexually transmitted infection and linked to the practice of oral sex. Studies have found higher sexual partner counts, oral sex prevalence, and increased number of lifetime sexual partners to be associated with AO-RRP. However, they also reported no significant difference in the number of lifetime oral sex partners

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when compared to controls, and instances where no prior oral sex or sexual partners were noted[12, 16]. An alternative hypothesis is that AO-RRP may represent the reactivation of latent infection acquired at the time of birth. However, JO-RRP and AO-RRP patients have been demonstrated to have different exposures to the proposed birth risk factors[12] as well as no discernible difference in birth history between AO-RRP patients and healthy controls[16].

Surgical treatment

In AO-RRP, the clinical course of the disease is highly variable but typically requires frequent surgical interventions. The average rate of surgeries per year is 4.4 and, although spontaneous remission can occur, chronic disease is the norm[17]. Paediatric patients with JO-RRP typically require an average of 5.1 surgeries per year, with a mean duration of disease of 4.4 years. Remission can occur at any age but is most likely in cases where the disease presents between 6-10 years and is confined to the larynx, with younger age of diagnosis (<5yo) being associated with more aggressive disease[18, 19]. Multiple modalities are available to surgically treat RRP under general anaesthesia. These include cold steel, microdebrider, coblation, CO_2 laser (10,600 nm), pulsed dye laser (PDL) (585 nm) and potassium titanyl phosphate (KTP) (532 nm), and blue-light laser (445 nm). There is growing evidence for the use of blue-light laser (445 nm) in an office-based laser treatment setting[20, 21]. In terms of efficacy, a retrospective study of 112 AO-RRP patients treated with KTP laser, CO_2 laser, or microdebrider found no significant difference in mean surgical intervals among the three treatment groups[22]. A further retrospective study of 194 AO-RRP patients treated with either CO_2 laser or cold steel resection found the method of treatment did not affect the rate of recurrence[23]. The United Kingdom (UK) RRP Registry of 1,208 procedures performed between April 2018 to August 2022 demonstrated that a wide variety of surgical approaches are used across the UK. Analysis from the registry regarding which surgical modalities are most effective in RRP has not yet been

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published, but the most common techniques employed were microdebrider, CO_2 laser, and radiofrequency ablation[24]. Repeated surgery at the same anatomic site carries a risk of complications such as mucosal scarring, webbing, impaired vocal cord mobility, subglottic and glottic stenosis. A recent systematic review and meta-analysis of 20 studies reported a complication rate ranging from 0% - 44.9%. The weighted average complication rate for CO_2 laser treatment was 0.16, for KTP laser was 0.04 and for microdebrider was 0.03[25].

Quality of life and economic burden

Recurrent respiratory papillomatosis imposes a substantial quality of life burden and economic strain. In the USA, the economic impact linked to non-cervical HPV types 6, 11, 16, and 18 was estimated to amount to $418 million annually[26]. The annual cost of treating a single case of JO-RRP has been estimated to range from $58,000 to $76115, and for AO-RRP to range from $5,000 to $11,000[27, 28]. A UK-based single-centre study reported an annual expenditure of £7,677 per AO-RRP patient[29]. RRP can also have a significant impact on a patient's quality of life. A recent study by So et al found that 65.7% of patients miss at least five workdays monthly, 79.5% reported social anxiety, and the average lifetime number of surgeries was 20[30]. The financial strain on patients is also evident, with over half allocating at least 5% of their annual income towards RRP-related medical care. This economic burden on healthcare systems and the considerable impact on patients' quality of life, emphasizes the pressing need for effective management strategies for RRP.

Malignant transformation and surveillance

While RRP is clinically a benign disease, the development of dysplasia and transformation to malignancy can occur. The rates of dysplasia reported in the literature range from 10-55% in AO-

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RRP and 0-10% in JO-RRP[31]. However, it is unclear if there is a typical progression from dysplasia to invasive malignancy in RRP. Factors that are thought to increase the risk for malignant transformation include previous radiotherapy, smoking, older age at diagnosis in AO-RRP, younger age at diagnosis in JO-RRP, and the HPV subtype[31, 32, 33]. The HPV subtypes 11, 16 and 18 are considered higher risk for malignant transformation[31], although it has still been reported to occur with HPV 6 infection[34]. With this in mind, there is evidence from case reports that the HPV subtypes present in the papilloma of an individual can change during the lifetime of their RRP disease. Doyle et al reported a case of JO-RRP where HPV 6 and 11 subtypes were detected initially, but with repeated biopsy over an 8-year period there was subsequent detection of HPV 16[35]. Fancello et al reported a case of AO-RRP where only HPV 6 was detected on biopsy at the three initial surgeries, but upon repeat surgery and biopsy 3 years later both HPV 6 and HPV 18 subtypes were detected[36]. This would suggest that repeat biopsies should be performed in patients both when there is clinical suspicion of progression or spread of disease, as well as at regular intervals as part of routine surveillance to detect any change in HPV subtype.

While the exact pathogenesis remains unclear, the risk of malignant transformation in laryngeal RRP is estimated to be 3-7% in adults and <1% in children[37]. However, up to 8.9% of patients with RRP will have pulmonary involvement, which carries a 32-fold increased lifetime risk of malignant transformation (range 11.7% to 16%) compared with the overall RRP population[38].

A clinical algorithm for screening and surveillance of pulmonary involvement in RRP, based on known risk factors, was developed by Pai et al and published in the Lancet in 2022[38]. The algorithm proposes performing a low-dose CT (LDCT) thorax scan in all AO-RRP patients at the time of initial diagnosis. In JO-RRP patients it recommends performing LDCT at 7 years in those with risk factors and at 18 years of age in those without. If no pulmonary nodules or cysts are detected, then the recommendation is for a surveillance LDCT thorax every 5 years. If a nodule or cyst is detected then,

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depending on its size, either close monitoring with interval surveillance LDCT or further diagnostic workup is required.

However, this clinical algorithm does not specifically address the management of patients where tracheal or proximal bronchial disease is identified at laryngo-tracheo-bronchoscopy. These patients may not necessarily have appreciable disease on cross-sectional imaging, but the presence of papilloma in these regions is a sign of more aggressive RRP disease[37] and confers a higher risk of progression to pulmonary involvement[39]. To our knowledge, there is no published recommendation for radiological surveillance in this patient cohort. Within our department, after discussion with specialist colleagues in radiology and respiratory, we have reached a consensus to perform an interval surveillance LDCT every 2 years in these patients.

As HPV infection is also a risk factor for the development of cervical and oropharyngeal malignancy, many patients worry RRP might lead to one of these types of cancer in future or put their sexual partners at risk. However, the few studies that have addressed concurrent infection in the head and neck and genital tracts suggest that oral oncogenic HPV infection occurs independently of cervical oncogenic HPV infection[40].

Current Adjuvant Treatments

While surgical intervention is the mainstay of management for RRP, approximately 20% of patients will require adjuvant treatments to achieve disease control[41]. Accepted criteria for considering initiation of adjuvant treatment include disease requiring ≥4 surgeries per year, rapid regrowth of lesions with airway compromise, or spread of disease to the distal airway[37].
The next paragraphs describe the different available adjuvant therapies in detail.

Gardasil Vaccine

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Gardasil is an HPV vaccine prepared from purified virus-like particles of the major capsid L1 protein that is found on the external surface of the virus[42]. The initial quadrivalent Gardasil vaccine was approved for use in 2006 against HPV strains 6, 11, 16, and 18. A 9-valent vaccine Gardasil-9 was subsequently approved for use against the additional strains of 31, 33, 45, 52, and 58 in 2014[43].

Gardasil vaccination leads to a persistent neutralizing antibody response and has been shown to have a profound effect on the prevention of RRP in countries where vaccination rates are high, such as in Australia where they demonstrated a significant decrease in the incidence of RRP from 0.16 to 0.02 per 100,000 children[44]. Furthermore, there is increasing evidence that national Gardasil vaccination programs are cost-effective and have a positive impact on public health by reducing the burden of HPV-related diseases, including HPV-associated cancer[45, 46, 47].

Gardasil vaccination is also thought to have a role as an adjuvant treatment. A 2019 systematic review and meta-analysis of 63 patients from 5 studies found that the mean interval between surgical procedures increased from 7.02 months to 34.45 months[48]. An updated meta-analysis in 2023 of 101 patients from 3 studies reported an estimated overall reduction of 0.123 recurrences or surgeries per month following Gardasil vaccination[49]. These findings suggest that HPV vaccination is effective as both a preventative measure and a therapeutic adjunct that can reduce the frequency of surgical interventions required by RRP patients.

The American Academy of Otolaryngology-Head & Neck Surgery released a position statement in 2021 supporting the use of Gardasil-9 vaccination in all RRP patients 9-45 years of age[50]. Its use in patients under 9 or over 45 years of age is considered "off-label" and therefore its use in these patients should be based on a shared-decision making process. While not contraindicated, there is a

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lack of evidence regarding the potential benefits of administration of the Gardasil-9 vaccination to patients with RRP who have previously received the quadrivalent Gardasil vaccine[51]. However, a large randomized, double-blinded, placebo-controlled trial published in 2015 investigated the effect of administering the Gardasil-9 vaccine to healthy adolescent and adult females who had previously received the quadrivalent Gardasil vaccine[52]. The study found that administration of the Gardasil-9 vaccine was safe and well tolerated, and led to seroconversion in >98% of participants with significant increases in antibody titres to all 9 HPV sub-types. The practice at our centre is to offer Gardasil-9 vaccination to both unvaccinated RRP patients and those who have previously received the quadrivalent Gardasil vaccine.

Intralesional Cidofovir

Cidofovir, a cytosine nucleotide analogue, exhibits its antiviral action by incorporating into the DNA chain of viruses and inhibiting the viral DNA polymerization process. Its long intracellular half-life leads to an antiviral effect that can last from several days to weeks. While the FDA approved Cidofovir for the treatment of cytomegalovirus (CMV) retinopathy in AIDS, it has been used off-label intralesionally for RRP since 1998[53].

Optimal timing and dosing for Cidofovir treatment in RRP lacks consensus. A 2013 study of 82 surgeons concluded that standalone indications for use included a requirement for ≥6 operations/year, increasing frequency of surgery, or extra-laryngeal spread in paediatric patients[54]. Initiation should be considered in patients who exhibited a combination of factors such as requiring ≥4 operations per year, persistent disease at the anterior or posterior commissures, and failure to respond to their current surgical regime. While most surgeons reported administering up to five

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injections to determine efficacy for the patient, some allowed up to 10 injections, and others did not observe a limit. Typical doses used are 20-40 mg (<4 ml) in adults and 20 mg (<2 ml) in paediatrics, with scheduled administration every 3 to 6 weeks. Safe total dosing limits for Cidofovir were deemed to be 3 mg/kg[54].

Regarding efficacy, a Cochrane review in 2012 of 92 publications found insufficient evidence to support the efficacy of intralesional Cidofovir over placebo[55]. The review included one randomized controlled trial published in 2008 of both adults (15) and children (4)[56]. A significant improvement in the Derkay Severity Score[3] (measure of disease extent) within the cidofovir and placebo groups was found at 2- and 12-month follow-ups. However, no significant difference was found between Cidofovir and placebo groups, nor any difference between groups in the number of procedures performed. However, a more recent literature review conducted in 2020 reported that intralesional Cidofovir achieved a complete response rate in 74% of 185 patients with AORRP and 56.5% of 85 patients with JORRP[57]. The mean concentration used in the studies was 7.5mg/ml, and the mean number of injections was 6, with 26 days between injections.

With regard to adverse effects, concerns have been raised regarding intralesional Cidofovir administration and the development of vocal fold scarring. While a porcine model showed no effect after a course of four injections of up to 5 mg (10 mg/mL) doses of intralaryngeal Cidofovir to the porcine vocal fold[58], a canine model showed dose-dependent irreversible atrophy and scarring of the canine vocal fold after a course of 12 injections of 20 mg (40 mg/mL) or 37.5 mg (75 mg/mL) doses[59]. Cidofovir is also contraindicated during pregnancy due to potential teratogenicity, and there have also been concerns raised about the risk of nephrotoxicity as well as possible carcinogenesis. With regards to nephrotoxic effects, these are known to be dose-dependent and have only been observed with high-dose systemic administration[60]. The concern regarding carcinogenesis stem from

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toxicology studies performed in rodents which were terminated early due to the development of mammary adenocarcinoma[61]. However, the total doses delivered were greater than the equivalent human systemic exposure received at the recommended dose for CMV retinopathy, and it should be noted that the development of mammary adenocarcinoma is a frequent occurrence in rodent pharmacological studies. These findings were not replicated in similar primate studies, albeit at intravenous doses equivalent to 0.7 times the human systemic exposure[62]. Concerns regarding a possible dysplastic effect of the drug were raised in a case, reported by Wemer et al in 2005, of progressive dysplasia seemingly associated with intralesional administration of Cidofovir in a patient with AO-RRP[63]. However, a subsequent international retrospective study of 635 AO-RRP patients demonstrated no differences in renal dysfunction or the incidence of upper airway and tracheal malignancies between Cidofovir and non-Cidofovir groups[64].

Intralesional Bevacizumab

Bevacizumab is a human monoclonal antibody that can bind to and inhibit vascular endothelial growth factor expressed on papilloma epithelium. This subsequently inhibits angiogenesis, which is thought to be a crucial factor in determining the rate of papilloma recurrence. Both systemic and intra-lesional administration have been described for the treatment of RRP, with the first systemic use reported in 2009[65].

The efficacy of Bevacizumab as a treatment option was assessed in a recent systematic review published in 2022[66]. A total of 64 patients were included from 15 case series or case report studies, with 54/64 of the patients having JO-RRP. When administered intralesionally, Bevacizumab was not found to be as effective as systemic administration, with only 62% (13 out of 21) of patients showing a prolongation in the post-treatment surgical interval (4-12 weeks) compared to the pre-treatment

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interval (2-6 weeks). The occurrence of side effects was discussed in 8 of the reported cases, with no side effects found.

The intra-lesional efficacy of Bevacizumab was further assessed in a randomised, placebo-controlled trial of 16 participants (5 children, 11 adults) comparing Bevacizumab to Cidofovir after cold steel papilloma resection[67]. Cidofovir exhibited a significant Derkay severity score decrease after one year (p=0.027), while Bevacizumab and placebo showed no significant changes. All treatment groups experienced a significant decrease in VHI score (p<0.001), attributed to surgical papilloma resection.

Systemic Bevacizumab

A 2021 Delphi study involving 70 international experts provided consensus statement on systemic Bevacizumab use in RRP[68]. The consensus suggested that age at surgery or at time of diagnosis should not be a deciding factor in the treatment of patients with RRP, with both paediatric and adult patients open to consideration. Disease characteristics that were supported by consensus or near-consensus included progressive and/or severe disease burden, disease in locations difficult to treat, need for tracheostomy due to disease burden, and increasing Derkay score over the preceding year.

Systemic Bevacizumab appears to be more effective than intralesional administration for the treatment of RRP[66]. Systemic treatment with Bevacizumab led to considerably longer surgical intervals in 95% (41 out of 43 cases) of patients post-treatment (3 – 17 months) compared to pre-treatment (1 – 8.6 weeks). In 55% (24 out of 43) of patients, no further surgical interventions were required during follow up. Side effects were observed in 44% (19 out of 43) of patients and included proteinuria, epistaxis, haemoptysis, hypertension, headache, thrombocytopaenia, hyperthyroidism, and nausea. However, these were all classified as mild and self-limiting.

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There is no universally adopted dosing protocol for the use of systemic Bevacizumab as an adjuvant treatment in RRP. One suggested regime following standard chemotherapy guidelines is a 10mg/kg target dose with infusions given initially every 3-4 weeks for 6 cycles, before a maintenance regime of infusions every 3 months for 2 years with surveillance laryngo-trachea-bronchoscopies[69].

Potential Future Adjuvant Treatments

While Cidofovir may block replication of HPV and Bevacizumab may block blood supply to the papilloma, neither result in clearance of the virus. Based on current understanding of antiviral immune responses, the only rational strategy to clear HPV-infected epithelial cells is through activation of the cytotoxic T-lymphocyte arm of the adaptive immune response. Activation of HPV immunity may clear the virus and cure the infection[70]. Immunotherapies, such as immune checkpoint blockade or engineered therapeutic vaccines, may provide a path toward tolerable and efficacious adjuvant immunotherapy for RRP

DNA Vaccines

DNA vaccine technology involves encoding the DNA sequence of a specific monoclonal antibody in a DNA plasmid, that is then delivered directly into cells of the body by electroporation. The host cells then manufacture the monoclonal antibody in vivo and stimulate an immune response[71]. DNA vaccines are a potentially promising novel therapeutic agent for the treatment of RRP and there is current clinical-stage research ongoing in this field.

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INO-3107 Vaccine

The biotechnology company INOVIO published the results of a phase 1 study of their product INO-3106 in 2020[72] and are currently undergoing Phase 1/2 clinical trial for their product INO-3107[73]. These products contain DNA immunotherapy designed to elicit targeted T-cell responses against HPV 6 and HPV 11. It is delivered by intramuscular injection followed by electroporation. The treatment induces activated CD4 T cells and activates CD8 T cells with lytic potential, and the percentages are similar for HPV 6 and HPV 11. The open-label, multi-centre trial enrolled 32 participants with RRP and administered four doses of the INO-3107 vaccine three weeks apart. For inclusion, participants must have required at least two surgical interventions/year for the past year for the removal of HPV 6 or HPV 11 associated papilloma. The primary outcome was the change in median number of surgical interventions in the year prior to Day 0 compared with the year following Day 0. In the reported preliminary results, 26 out of 32 (81.3%) of participants had a significant reduction in the number of surgical interventions required, with a median decrease of 3 surgical interventions. Ten out of these 26 participants required no surgical intervention during the follow up period. The vaccine was shown to induce T-cell responses against both HPV 6 and HPV 11. This was still observed at week 52, suggesting a persistent cellular memory response. The INO-3107 vaccine was generally well tolerated, with all patients completing the follow up. The results support further investigation of INO-3107 plus electroporation, with a confirmatory trial currently being planned as part of INOVIO's Biological Licence Application submission to the U.S. Food and Drug Administration[74].

NIH PRGN-2012 Vaccine

This vaccine, developed by Precigen Inc., is a subcutaneous injection of gorilla adenovirus encoding HPV DNA designed to elicit immune responses directed against HPV 6 and HPV 11. A preclinical study in 2021 showed that it induces low risk HPV antigen-specific responses in in-vitro stimulation of peripheral T lymphocytes from patients with RRP. In-vivo therapeutic vaccination of mice bearing established HPV6 E6 expressing tumours resulted in HPV 6 E6-specific CD8+ T-lymphocyte immunity of sufficient magnitude to induce tumour growth delay[75]. A non-randomised, phase 1/2 safety and tolerability study is in progress and estimated to be completed in 2026[76].

Pembrolizumab

Pembrolizumab is a humanized monoclonal antibody that acts as a PD1 receptor inhibitor on T-cells[77]. By inhibiting PD1 receptors, Pembrolizumab leads to activation of T-cells and an immune response against potentially abnormal cells, such as tumour cells or the HPV-infected cells in RRP. The efficacy and safety of Pembrolizumab monotherapy is currently being investigated in a phase 2 clinical trial of 21 patients (10 JO-RRP, 11 AO-RRP, 62% trachea-pulmonary involvement)[78]. Preliminary results from the trial found that 57% of patients (7/10 JO-RRP, 5/11 AO-RRP) had a partial response. Stable disease was reported in 7 out of 21 patients. No complete responses were observed. Surgical interventions were reduced by a mean of 7 operations/year in patients treated with Pembrolizumab for >12 months. However, only 62% (13/21) patients completed the 24 months of treatment, with reasons for discontinuation including disease progression, treatment-related adverse events, and study withdrawal. Overall, the preliminary results suggest that while Pembrolizumab reduced the need for routine surgical intervention there appears to be variable response in the reduction of tumour burden.

Discussion

Among the available adjuvant treatments, systemic Bevacizumab appears to be the most effective, consistently resulting in extended surgical intervals post-treatment, and notably, a substantial proportion of patients experiencing no further need for surgical interventions[66]. In comparison, intralesional Bevacizumab exhibits a less pronounced impact, achieving a smaller increase in surgical intervals in a lower percentage of patients[66, 67]. Systemic Bevacizumab is associated with a risk of side effects that is not seen with intralesional administration. While these tend to be mild or moderate in grade, clinical and biochemical monitoring of patients throughout the treatment course and follow-up period is required to promptly recognise and address any adverse effects[66]. While evidence supporting a reduction in the frequency of surgical procedures after intralesional Cidofovir is limited, it demonstrates a reasonable complete response rate, particularly in patients with AO-RRP[57]. Concerns have been raised regarding possible nephrotoxic and oncogenic effects of Cidofovir, but these risks appear to be associated only with higher-dose systemic administration with no existing evidence that strongly supports an association between intralesional Cidofovir and renal dysfunction or dysplasia[60, 64]. The Gardasil vaccine has been demonstrated to be valuable as both a preventative measure and therapeutic adjunct that can lead to reduced recurrence rates and prolonged surgical intervals. The widespread vaccination of pre-adolescent children is expected to reduce the incidence of HPV genital warts. This, in turn, will decrease the risk of vertical HPV transmission, ultimately lowering the incidence of JO-RRP and overall RRP[79].

There are a number of potential future immunotherapy and DNA vaccine-based adjuvant treatments on the horizon. The most promising of these is the INO-3107 DNA vaccine, with phase 2 trials reporting a significant reduction in the average number of surgical interventions for the majority of

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participants, with some requiring no surgical interventions during the follow-up period, as well as persistent T-cell responses[73]. Further plans are currently being developed for a confirmatory trial.

The economic burden associated with RRP, and the financial cost of treatment is considerable. While a number of adjuvant treatments are available, the financial implications of each for a healthcare system should be taken into consideration. This is particularly important in government-funded healthcare settings such as the National Health Service in the UK, where the cost of treatment can significantly limit access and availability. Whilst administration of the Gardasil-9 vaccine has been reported to cost £259[29], the estimated cost of systemic Bevacizumab is >£1500 per infusion based on a 70kg patient at a 10 mg/kg dose[80]. To commence a patient with RRP on systemic Bevacizumab in the NHS a clinician is required to complete an individual funding request that specifically explains the clinical circumstances that warrant this treatment.

Based on the current literature, we have developed a management guideline for adult patients with RRP to be used in our tertiary centre in the UK [Figure 2]. The guideline aims to assist with the identification of patients who have resistant disease where adjuvant treatments should be considered. The presence of severe disseminated disease or pulmonary involvement, and thus the risk of malignant transformation, is used to determine whether adjuvant treatment with intralesional Cidofovir or systemic Bevacizumab is likely to be more beneficial for the individual patient. For each of these adjuvant treatments, our guideline details the pre-treatment work-up required, the dosing regime, and the follow-up surveillance required.

Limitations

We recognise that our review has some limitations in that we did not perform a systematic review and meta-analysis. However, lack of uniformity in study designs, small sample sizes, and variations in treatment protocols and outcome measures across different studies lead to inherent heterogeneity of the available data that would have limited the value of doing so. To improve our understanding of the indications and optimal dosing regimens, future prospective studies, including randomised controlled trials, comparing different adjuvant treatments with standardised outcome measures would be invaluable.

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Conclusions

Recurrent respiratory papillomatosis is a rare but chronic disease that can require lifelong treatment that has a significant impact on quality of life as well as placing a substantial economic burden on a healthcare system. This review provides a detailed examination of current and potential future adjuvant treatments for RRP and proposes a management guideline for adult patients based on the current literature. Further prospective studies and randomized controlled trials are essential to refine treatment and enhance our understanding of optimal dosing regimens for these adjuvant therapies.
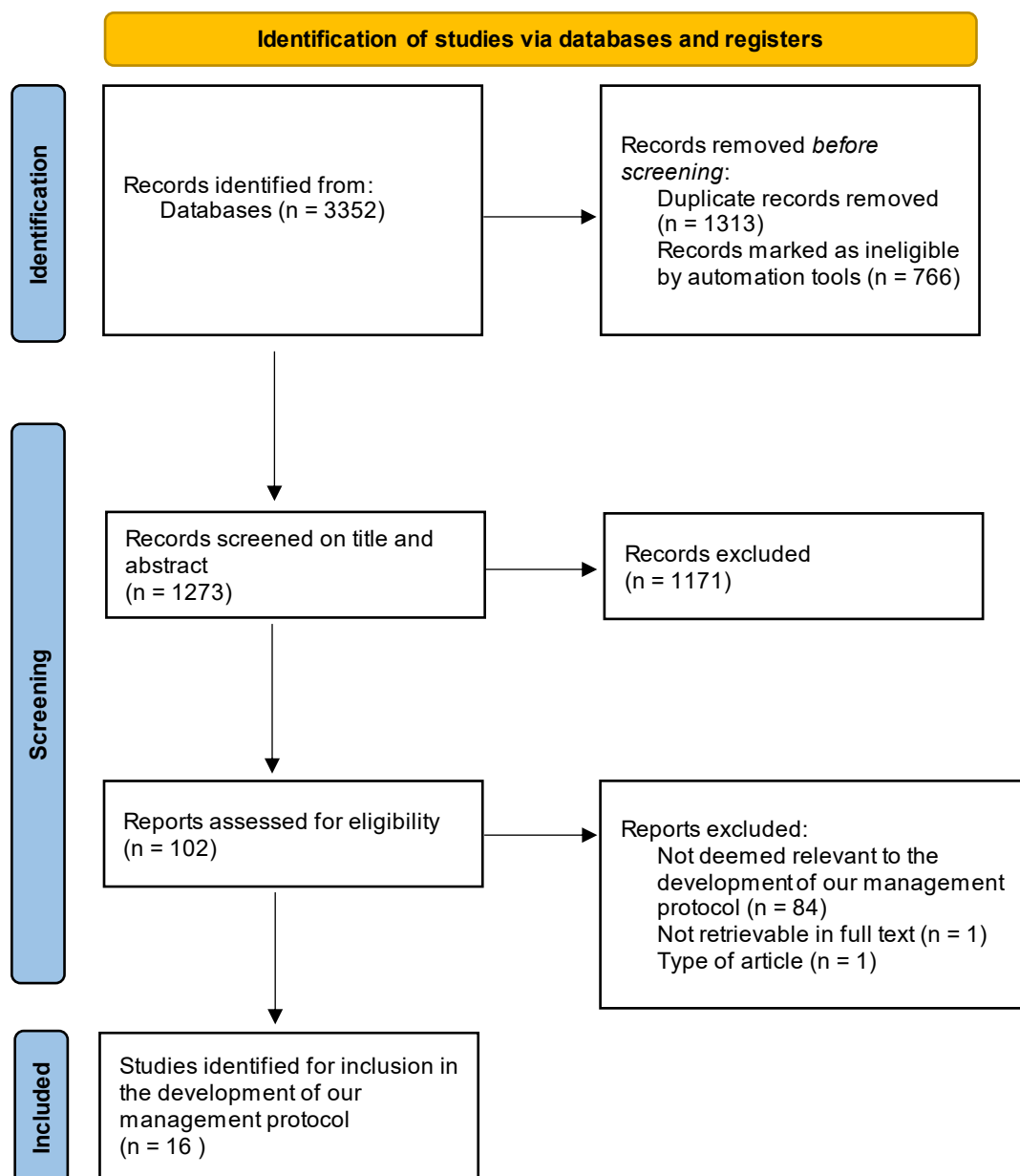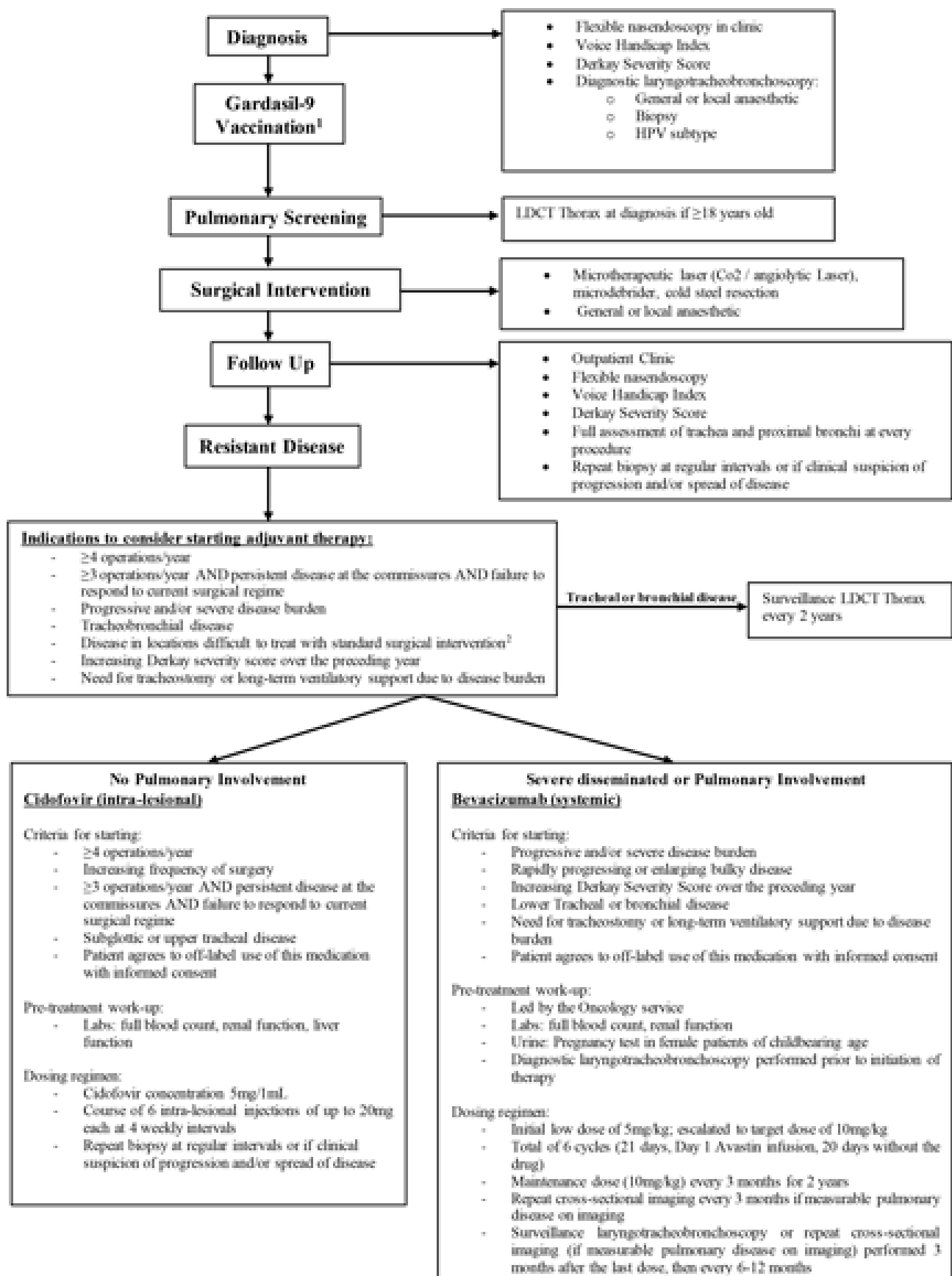
Competing Interests

The authors declare none.

Figure 1: Flow diagram of screened and included studies identified via database search

Figure 2: Recurrent respiratory papillomatosis adult management guideline

Diagnosis
- Flexible nasendoscopy in clinic
- Voice Handicap Index
- Derkay Severity Score
- Diagnostic laryngotracheobronchoscopy:
  - General or local anaesthetic
  - Biopsy
  - HPV subtype

Gardasil-9 Vaccination[1]

Pulmonary Screening
- LDCT Thorax at diagnosis if ≥18 years old

Surgical Intervention
- Microtherapeutic laser (Co2 / angiolytic Laser), microdebrider, cold steel resection
- General or local anaesthetic

Follow Up
- Outpatient Clinic
- Flexible nasendoscopy
- Voice Handicap Index
- Derkay Severity Score
- Full assessment of trachea and proximal bronchi at every procedure
- Repeat biopsy at regular intervals or if clinical suspicion of progression and/or spread of disease

Resistant Disease

Indications to consider starting adjuvant therapy:
- ≥4 operations/year
- ≥3 operations/year AND persistent disease at the commissures AND failure to respond to current surgical regime
- Progressive and/or severe disease burden
- Tracheobronchial disease
- Disease in locations difficult to treat with standard surgical intervention[2]
- Increasing Derkay severity score over the preceding year
- Need for tracheostomy or long-term ventilatory support due to disease burden

Tracheal or bronchial disease → Surveillance LDCT Thorax every 2 years

No Pulmonary Involvement
Cidofovir (intra-lesional)

Criteria for starting:
- ≥4 operations/year
- Increasing frequency of surgery
- ≥3 operations/year AND persistent disease at the commissures AND failure to respond to current surgical regime
- Subglottic or upper tracheal disease
- Patient agrees to off-label use of this medication with informed consent

Pre-treatment work-up:
- Labs: full blood count, renal function, liver function

Dosing regimen:
- Cidofovir concentration 5mg/1mL.
- Course of 6 intra-lesional injections of up to 20mg each at 4 weekly intervals
- Repeat biopsy at regular intervals or if clinical suspicion of progression and/or spread of disease

Severe disseminated or Pulmonary Involvement
Bevacizumab (systemic)

Criteria for starting:
- Progressive and/or severe disease burden
- Rapidly progressing or enlarging bulky disease
- Increasing Derkay Severity Score over the preceding year
- Lower Tracheal or bronchial disease
- Need for tracheostomy or long-term ventilatory support due to disease burden
- Patient agrees to off-label use of this medication with informed consent

Pre-treatment work-up:
- Led by the Oncology service
- Labs: full blood count, renal function
- Urine: Pregnancy test in female patients of childbearing age
- Diagnostic laryngotracheobronchoscopy performed prior to initiation of therapy

Dosing regimen:
- Initial low dose of 5mg/kg; escalated to target dose of 10mg/kg
- Total of 6 cycles (21 days, Day 1 Avastin infusion, 20 days without the drug)
- Maintenance dose (10mg/kg) every 3 months for 2 years
- Repeat cross-sectional imaging every 3 months if measurable pulmonary disease on imaging
- Surveillance laryngotracheobronchoscopy or repeat cross-sectional imaging (if measurable pulmonary disease on imaging) performed 3 months after the last dose, then every 6-12 months

[1] 3 doses of Gardasil-9 vaccine given intramuscularly at 0, 2, 6 months. Consider offering Gardasil-9 vaccination even if a patient has previously received the quadrivalent Gardasil vaccination.
[2] Tracheal, bronchial, pulmonary, persistent disease at the commissures.
LDCT: low-dose computed tomography. HPV: human papillomavirus.

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Table 1: Articles identified in the database search relevant to the development of the management guideline

#	Author	Year	Study Design	Adjuvant Treatment / Topic	N	Outcome measures	Follow Up / Study Period
1	Ablanedo-Terrazas et al[64]	2022	Randomised, double-blind, placebo-controlled trial	Intralesional Cidofovir Intralesional Bevacizumab	11 AO-RRP 5 JO-RRP	Derkay severity score Voice Handicap Index	1 year
2	Armstrong et al[18]	1999	Prospective, multi-centre, case series	Surgical interventions Adjuvant treatments	399 JO-RRP	Frequency of surgical interventions Disease progression Adjuvant treatments Need for tracheostomy	2 years
3	Benedict et al[43]	2021	Descriptive review	Management of RRP	N/A	N/A	N/A
4	Derkay et al[51]	2013	Cross-sectional study, web-based clinician survey	Intralesional Cidofovir	801 AO-RRP 447 JO-RRP	Indications Administration Associated adverse events	N/A
5	Derkay et al[2]	2008	Descriptive review	Management of RRP	N/A	N/A	N/A
6	Fortes et al[5]	2017	State-of-the-art review	Management of RRP	N/A	N/A	N/A
7	Gazia et al[54]	2020	Systematic review	Intralesional Cidofovir	185 AO-RRP 85 JO-RRP	Concentration used Number of injections Injection interval Therapeutic response Side effects Progression to dysplasia	N/A
8	Goon et al[49]	2023	Systematic review and meta-analysis	HPV vaccine	101 AO-RRP	Frequency of surgery Rate of recurrence	N/A
9	Hock et al[22]	2022	Retrospective, multi-centre, case series	Surgical interventions Adjuvant treatments	44 AO-RRP 68 JO-RRP	Derkay severity score Progression to dysplasia	10 years
10	Liu et al[25]	2023	Systematic review and meta-analysis	Safety of surgical interventions	576 AO-RRP 419 JO-RRP	Intra-operative complications Post-operative complications	N/A
11	McMurray et al[53]	2008	Randomised, double-blind,	Intralesional Cidofovir	14 AO-RRP 5 JO-RRP	Derkay severity score Voice Handicap Index Health-Related Quality of Life	1 year

			placebo-controlled trial		Frequency of surgical interventions	
12	Pogoda et al[63]	2022	Systematic review	Intralesional Bevacizumab Systemic Bevacizumab	10 AO-RRP 54 JO-RRP	Treatment dose and interval Frequency of surgical interventions Derkay severity score Complications	N/A
13	Rosenburg et al[48]	2019	Systematic review and meta-analysis	HPV vaccine	133	Frequency of surgical interventions	N/A
14	Sidell et al[65]	2021	Delphi method-based survey	Systemic Bevacizumab	N/A	Patient characteristics Disease characteristics Treating centre characteristics Prior treatment characteristics Prior work-up	N/A
15	Tjon Pian Gi et al[61]	2013	Retrospective, multi-centre, cohort study	Intralesional Cidofovir	AO-RRP 517 JO-RRP 118	Nephrotoxic side effects Neutropenic side effects Oncogenic side effects	14 years
16	Welschmeyer et al[10]	2021	Systematic review	Epidemiological factors	N/A	Risk factors associated with RRP Patient demographics HPV immunological characteristics Clinical course Psychosocial factors	N/A

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