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TREATMENT OF DESCENDING NECROTIZING MEDIASTINITIS ASSOCIATED WITH DEEP NECK INFECTIONS: AN ACCOUNT OF THE MOST CURRENT DATA

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ABSTRACT

Deep neck infections (DNIs) are life-threatening diseases that represent the crossroads between maxillofacial surgery and otorhinolaryngology. A DNS has the potential to extend into the mediastinum, where it can trigger a very dangerous disease known as descending necrotizing mediastinitis (DNM), which has a high mortality rate. This article reviews the etiology, bacteriology, clinical manifestations, diagnostic techniques, and management approaches for DNIs and DNM. We emphasize the importance of early diagnosis by imaging studies, such as computed tomography (CT), and a multidisciplinary approach utilizing antibiotics coupled with surgical intervention for the management of these life-threatening diseases.

KEYWORDS: *Deep neck infection, descending necrotizing mediastinitis, diagnosis, multidisciplinary treatment, surgical treatment*

INTRODUCTION

Deep neck infections (DNIs) are significant emergencies that can easily spread to the mediastinum, a complication referred to as descending necrotizing mediastinitis (DNM). The cervical fascial planes play a crucial role in the spread of these DNIs (1,2). Thus, knowledge of the anatomy of these fascial planes is crucial for the successful diagnosis and treatment of DNIs.

DNIs can be caused by odontogenic infections, pharyngitis, salivary gland infections, trauma, or foreign bodies (3-5). These latter infections spread into the mediastinum when they overcome the natural resistance of the fascial planes. Cellulitis, abscess, and phlegmon are different stages of the infection and each has a different management approach (4,5).

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The cervical fascia can be superficial and deep, creating retropharyngeal and parapharyngeal spaces, among others, that may become infected and serve as pathways for the dissemination of infection. Knowledge of such structures is important to the clinicians for the planning of appropriate treatment modalities and preventing further complications (5,6).

DISCUSSION

Etiopathology

Odontogenic and pharyngeal infections are the most common causes of DNIs, though there are other causes too, including trauma, cancer, and iatrogenesis following operations such as endoscopy (7-9). The infection usually extends to the salivary gland, buccal, pharyngeal, and dental mucosa from the initial site by hematogenous or lymphatic routes of dissemination (10,11). The submandibular space is reported to be the most commonly affected space, followed by the parotid and sublingual spaces in many cases (11,12).

DNI usually presents with a mixed bacterial flora comprising both aerobic and anaerobic bacteria (13-15). The most common pathogens found are *Streptococcus viridans* and *Staphylococcus aureus*, but in immunocompromised hosts, like in the case of diabetics, and human immunodeficiency virus (HIV) and cancer patients, *Klebsiella* and other Gram-negative bacteria are also prevalent (16,17). Because these diseases are serious and take root with rapid growth, affected patients must be admitted to a medical facility immediately. DNM is a condition that is present in 3% of DNI cases and comes with a mortality rate of 50%, which is due to inadequate drainage and delayed diagnosis following untreated DNIs (18-21) (Table I).

Table I. *A literature review of the etiological factors of mediastinal involvement of deep neck infection (DNI).*

	Mithos et al. 2007	Roccia et al. 2007	Ridder et al. 2010	Kocher et al. 2012	Celakovsky et al. 2014	Kimura et al. 2020	Gehrke et al. 2022	Ho et al. 2022
Odontogenic	63%	39,1%	11,1%	5,9%	40%	5%	15,56%	38%
Pharyngo-tonsillar	37%	60,9%	46,7%	82,3%	33,5%	33%	55,56%	19,1%
Retropharyngeal abscess	-	-	-	-	-	5 %	-	19,1%
Other	-	-	42%	-	6,5%	18%	28,88%	-
Unknown	-	-	-	11,8%	20%	39%	-	23,8%

Clinical Diagnosis

The most common symptoms of deep throat infections include neck pain and swelling, although fever and odynophagia are frequent in diverse studies (22,23). Otalgia, dysphonia, dysphagia, trismus, and dyspnea are some symptoms that are specific to the affected area. Pain, often dental or swallow-related, is an early symptom. Acute pain and dysphagia occur when the infection is at an advanced stage (24-26). Dysphonia and dyspnea may accompany pharyngeal and laryngeal infections with a sudden decline in the patient's status. More severe cases can also demand tracheotomy because limited mobility and trismus occur as a result of swelling and infiltration of neck tissues. Fever is also commonly present, although immunocompromised patients may show no fever despite significant invasion of tissue (26-28).

It is commonly observed that inadequately treated infections of the cervico-mediastinal may result in serious sequelae like dyspnea, spontaneous fistulization, and mediastinitis. Mediastinum infection produces symptoms such as erythema of the skin, respiratory distress, and toxic-septic shock. Other adverse effects include low oxygen saturation, tachycardia, hypertension or hypotension, and sweating (29,30). If left untreated, many fascial spaces involved in cervical suppuration can result in severe pneumonia, cardiac issues, and renal failure, all of which carry a significant mortality rate.

A physical examination is done by examining the neck and palpating it to observe soreness, edema, and erythema (31,32). A buccopharyngoscopy evaluates the airway, throat, and mouth. The examination can diagnose edema, erythema, and dental problems; the airway can only be evaluated with fiberoptic laryngoscopy. Tracheotomy or cricothyroidotomy may be necessary in severe cases due to the possibility of respiratory arrest, which causes symptoms such as dysphagia,

toxicity, fever, and stiff neck. If the infection extends to the mediastinum, mediastinitis with excruciating chest pain could lead to mortality (32-34).

Symptoms related to infections in the lateral pharyngeal spaces include fever, pain, rigidity, and possibly trismus, depending on the compartment involved. While the posterior compartment has mild swelling, the anterior compartment is infected, producing symptoms of infection and neck pain from muscle spasms. Common systemic manifestations are results of infection of the parotid gland (eg. swelling), while severe ones can include jugular vein thrombosis and erosion of the carotid artery, among others. If left untreated, necrotizing fasciitis is a dangerous infection which can spread along the plane of a tissue and cause tissue death and a sepsis systemically (35-37).

Dysphagia, chest pain, and fever are the early symptoms most frequently encountered in case of perforations from trauma of the crico-pharynx. Other signs such as subcutaneous emphysema, tachycardia, and respiratory distress may be encountered during the clinical examination (38-40). Although the initial symptoms in deep throat infection are moderate, diagnosis management must consider the presence of comorbid conditions such as diabetes, HIV, cancer, and autoimmune diseases. These are the groups of patients with increased risk of serious complications (41-45).

Paraclinical Diagnosis

Laboratory tests include leukocyte count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and renal function, all of which are very important in delineating the extent of infection and guiding treatment. Imaging techniques are necessary to identify the extent of DNI, especially computed tomography (CT) (45-47). Compared with CT, magnetic resonance imaging (MRI) has the disadvantage of being more expensive and having longer scanning times. However, it yields high-resolution soft tissue images (48-50). CT scans also have their own shortcomings, with a false positive rate of about 10%, and a false negative rate of about 13%. MRI is preferred in complicated cases that might involve vascular abnormalities. Although chest X-rays are useful in the differential diagnosis of conditions like pneumonia and pleural effusion, CT remains the standard when mediastinal involvement is to be reviewed (50,51).

Treatment of Deep Neck Infection (DNI) Associated with Descending Necrotizing Mediastinitis (DNM)

1. *Airway Management*

   One of the major issues in DNI is the acute obstruction of the airways; this is particularly critical when more than one site is involved with the infection (52-54). Many times, tracheotomy or orotracheal intubation is required (55,56). When this is not possible by any of the above methods, emergency cricothyrotomy is the method of choice for securing the airway. Due to the inherent risks involved for the airway, the management of these conditions requires a multidisciplinary team of physicians specializing in ear, nose, and throat (ENT), anesthesia, and critical care (57-60).

2. *Medical Treatment*

   As soon as possible, empirical antibiotic therapy should begin, taking a broad spectrum of bacteria in consideration, until the results of the culture allow for a more focused approach (61-63).

   Generally used regimes include penicillin plus beta-lactamase inhibitors or cephalosporins plus metronidazole or clindamycin for anaerobic coverage. In cases suspected to involve methicillin-resistant *Staphylococcus aureus* (MRSA) or when the patient is immunocompromised, the addition of Vancomycin is suggested (64). Gentamicin is often added to cover for Gram-negative bacteria such as *Klebsiella* in diabetic patients. Dosages of antibiotics are modified once the culture and sensitivity results are available (65).

3. *Directed Antibiotic Therapy*

   Short-term use of steroids is utilized to control airway inflammation and reduce edema (66). Generally, this is not advisable for diabetic patients due to the risk of hyperglycemia. Supportive care treatment in a critical care setting includes oxygen therapy, fluid control, and monitoring (66-68).

4. *Systemic Therapy*

   As soon as possible, empirical antibiotic therapy must begin with a broad spectrum of bacteria in mind, until the results of the culture lead to a narrower approach (61-63).

5. *Surgical Treatment*

   The appropriate surgical intervention in DNIs, which can be life-threatening, requires an understanding of the complex anatomy of the neck spaces (68,69).

The site of infection gives indications about the microorganisms involved and the source of infection, thereby helping aid empirical antibiotic therapy. The extension of infection to many cervical compartments necessitates aggressive surgical draining and debridement. Drainage usually entails incisions in the area of the sternocleidomastoid muscle (64); CT imaging studies are necessary to position the tissues that are involved. If the disease process involves the muscles of the peripharynx or perilarynx, drainage must be very carefully carried out with the fingers (70).

6. Minimally Invasive Surgical Treatment

The role of minimally invasive procedures like drainage and radiologically guided aspiration versus non-surgical treatment remains controversial (70-72).

For patients who have a well-defined unilocular abscess with no compromised airway, the percutaneous echo-guided drainage is a useful treatment modality. Some of the advantages of minimally invasive procedures such as ultrasonography and CT-guided needle aspiration include less scarring and faster healing. This approach is more frequent in cases involving minors (73). However, in adults, if the surgery is delayed longer than two days after admission to the hospital, the morbidity and mortality rate is higher (74-76).

7. Surgical Treatment by External Incisional Approach

The external cervical route is usually followed, especially in deep infections of the retropharyngeal space. Reasons to perform surgery include obstruction to the airway, septicemia, and failure of improvement after 48 hours of antibiotic treatment (77,78). Deep space infections are subjected to surgical drainage from the outside; single-space abscesses are treated with minimum surgery. Tracheal compression causing severe respiratory failure may require tracheotomy with local anesthetic (79-81).

Saline irrigation inhibits infection when the infected areas are left open for investigation and further debridement after the surgery. Extensive incisions and drainage may facilitate the creation of a more favorable site for healing in cellulitis cases which present various spaces. Some authors also propose that independent incisions be carried out only for drainage, as well as tracheotomy, to prevent the extension of infection to the mediastinum (82-84) (Table II).

Table II. *Comparison of Surgical Techniques.*

Technique	Indication	Advantage	Disadvantage
Open Drainage	Multi-space involvement	Thorough exploration	Invasive
Minimally invasive	Single, localized abscess	Faster recovery	Limited application

Multidisciplinary Approach and Complications

The management of DNIs, especially complicated cases or in patients with comorbidities, involves input from experts in ENT, maxillofacial surgery, infectious diseases, radiology, thoracic surgery, and intensive care (84,85). The experts almost all agree that surgical drainage is indicated in the effective management of these infections for the procurement of microbiological samples for further treatment (86,87).

Laryngeal infections can extend to involve the thyroid gland and may require surgical drainage. In Ludwig's angina, securing the airway and commencing antibiotics often requires tracheotomy. If there are no collections noted on a CT, then it is possible to manage this condition with antibiotic therapy alone; otherwise, surgery becomes necessary (87,88).

In cases of lateral pharyngeal infections, drainage is usually performed in order to avoid further complications. Retropharyngeal infections may need a transcervical approach or may require a joint ENT-thoracic team for their surgical management. Such infections tend to extend to vital structures such as the meninges or lungs. Therefore, the mortality rate associated with them can be quite high if there is any delay in management (88-90).

Descending Necrotizing Mediastinitis (DNM)

Failure to drain DNIs may lead to rapid deterioration and sepsis. DNM necessitates urgent multidisciplinary management involving ENT, thoracic surgery, and intensive care specialists. Early interventions, including airway protection and drainage, are critical to reduce complications (90-93). There are various approaches to mediastinal drainage; the video assisted thoracic surgery (VATS) approach is always preferred because it gives a very good view and is minimally traumatic, though at the cost of some risk of pleural contamination (53,93-97) (Table III).

Table III. *Classification and Treatment of Deep Neck Infections (DNIs).*

Type of infection	Description	Treatment
Cellulitis	Inflammation without suppuration	Antibiotics and monitoring
Abscess	Localized suppurative infection	Surgical drainage and antibiotic therapy
Phlegmon	Diffuse infection without boundaries	Surgical drainage and antibiotic therapy

CONCLUSIONS

Most DNI and DNM lesions originate in the otorhinolaryngological (ORL) and oro-maxillofacial (OMF) areas. Mucosal contamination, which is mucosal damage due to endoscopic procedures or orotracheal intubations, results primarily from dental, buccal, pharyngeal, laryngeal, submaxillary, or parotid glandular inflammatory origins but also from iatrogenic sources. A lymphatic or hematogenous route spreads the infection.

Airway evaluation must be performed first, and any sign of respiratory distress or imminent airway compromise must be considered an emergency to be aggressively treated. This is followed by empirical broad range antibiotic treatment, with adjustments based on the reports of bacterial culture and sensitivity. Because of advances in anesthesia, antibiotics, surgery, diagnostic techniques, and intensive care protocols, the death rate among patients with DNI and DNM has been significantly reduced within the past 20 years.

Appropriate intensive and early therapy can be initiated from the findings in CT to prevent the infection from spreading into DNM. This may be followed by a dynamic CT follow-up at 48–72 hours after the initial surgical operation, which may show the need for a secondary procedure to drain any residual abscess or to remove devitalized tissue. When DNM is treated with DNI treatment by a multidisciplinary team, sepsis, death, and major sequelae are reduced.

Author Contributions

Conceptualization, A.M., F.I., A.M.I., D.C. and G.D.; methodology, A.M.I., D.C., G.D., and A.M. software, F.I., G.D., A.M.I., D.C. and A.M.; validation, F.I., A.M.I., G.D., A.M. and D.C. formal analysis, A.D.I., A.M.I., A.M., D.C. and F.I.; investigation, A.M., D.C., A.M.I., F.I. and G.D.; resources, A.M., A.M.I., D.C., F.I. and G.D.; data curation, G.D., D.C., A.M., A.M.I. and F.I.; writing original draft preparation, A.M., A.M.I., D.C. and F.I.; writing review and editing, F.I., A.M., D.C., A.M.I. and G.D.; visualization, D.C., A.M., A.M.I., F.I. and A.M.I.; supervision, G.D, F.I., A.M., A.M.I. and D.C.; project administration, A.M., D.C., F.I., A.M.I. and G.D.. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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COMPLETE INHALATION TREATMENTS WITH BICARBONATE-SULPHATE-ALKALINE-EARTHY MINERAL WATER IN THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AGGRAVATED BY ALLERGIC RHINITIS

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ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is a fairly widespread disease, affecting approximately 300 million people worldwide. Although it may be a highly disabling disease in itself, COPD tends to manifest in an even more aggressive and uncomfortable way when associated with the presence of upper respiratory tract affections, as in the case of Allergic Rhinitis (AR). Therapeutically, thermal respiratory treatments would seem to possess anti-inflammatory and decongestant properties capable of improving health both in the presence of COPD and AR. Therefore, we aimed to study the efficacy of a protocol called Complete Inhalation Treatments (CIT), based on a combination of inhalations and aerosol with bicarbonate-sulphate-alkaline-earthy mineral water from the Castelnuovo della Daunia Thermal Medicine Center integrated with non-invasive mechanical ventilation. We recruited 24 patients (12 males and 12 females, mean age 63 years) affected by COPD aggravated by fall AR. Patients were evaluated before (T0) and after (T1) the execution of a protocol of 12 total CIT sessions carried out over the course of 2 weeks, using the Medical Research Council dyspnea scale (MRC) and COPD Assessment Test (CAT). At the end of the study, a significant reduction in MRC and CAT scores was detected, reaching mean values below the pathological cut-off of ≥2 for MRC and ≥10 for CAT respectively. Therefore, the CIT protocol is effective in improving the respiratory symptoms of patients with COPD aggravated by AR. New, broader and more in-depth studies on the topic are desirable.

KEYWORDS: *Rehabilitation, physical therapy, thermal care, balneotherapy, mineral water, chronic obstructive pulmonary disease, seasonal allergic rhinitis*

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a fairly common disease, affecting approximately 300 million people worldwide (1) and it is estimated that within 30 years it could become the third leading cause of death (2). It is

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also estimated that a percentage ranging from 70% to 80% of patients present the pathology in an insidious and/or undiagnosed form (3). COPD is a disease characterized by obstructed ventilatory patterns, often of a slowly progressive but partially reversible type, determined by environmental factors, in particular smoking, mixed with genetic factors that are not yet fully understood (1). Beyond its well-known symptomatology, it must be considered that an interaction between COPD and other pathologies capable of exacerbating its symptoms and severity is increasingly being observed; among these comorbidities, particular attention should be given to the presence of seasonal Allergic Rhinitis (AR) in patients affected by COPD (4). AR is one of the most frequent upper airway diseases: it is an immune and inflammatory reaction to exposure to pathogens of various nature (5) characterized, above all, by the presence of rhinorrhea and nasal congestion due to swelling of the nasal mucosa (5). More and more research is attributing to AR and other upper respiratory diseases, such as asthma and chronic rhinosinusitis, the ability to markedly worsen the quality of life and symptoms of patients affected by COPD (5,6). These pathological associations have led some authors to indicate the presence of rhinitis as a potential marker of COPD-Asthma Overlap Phenotype (7). Other research highlights how rhinitis could be part of a pathological vicious circle whereby COPD itself predisposes to the onset of rhinitis, at least in its non-allergic form (8), which in turn may worsen the symptoms of COPD.

Among the less invasive treatment methods in the field of upper respiratory tract pathologies, which can also include AR, we can identify thermal therapy and spa treatments (9,10). Thermal medicine has repeatedly proven useful in the treatment of various types of pathologies, by virtue of the specific properties of the waters from the various thermal environments, as well as the advances in technologies and therapeutic methods that fall within the scope of thermalism as a natural treatment method and synonymous with well-being (11). Also in our experiences, thermal medicine, in the form of Integrated Thermal Care (ITC) approach, has proven useful in multiple complex pathological contexts, from neurological and musculoskeletal disabilities (12,13) to the treatment of Long COVID-19 Syndrome (14).

Among the methods applicable in the field of thermal medicine, we often see the use of Complete Inhalation Treatments (CIT) which are based on assisted inhalations, insufflations, aersol and noninvasive ventilations which exploit the properties of thermal waters and their specific mineral compositions in the treatment of respiratory and otorhinolaryngologic disorders (9,15,16).

Therefore, based on what is highlighted in the literature on the topic and on our experiences in the field of thermal medicine, we decided to evaluate the effectiveness of the CIT protocol in improving the health status of patients affected by COPD aggravated by the presence of fall AR, typically associated with the presence of pollens (such as ragweed and wormwood), environmental molds and dust mites in the autumn period (17).

MATERIALS AND METHODS

The present research is a small clinical trial carried out at the Castelnuovo della Daunia Thermal Medicine Center (Castelnuovo della Daunia, Italy) from September to November 2023.

The rehabilitation protocol to which the patients were subjected is safe, as all the therapeutic procedures applied to patients comply with the safety regulations in force in the country where the study was carried out; the protocol is accessible to all patients who do not highlight specific contraindications to the initial clinical evaluation necessary for all patients who access the facility of the study. Clinical research was performed in accordance with the Helsinki Declaration and Good Clinical Practice standards (18). All participants signed the informed consent for the procedures. All the evaluation and treatment methods used for this study, as well as the actual application procedures, are commonly used in the clinical-rehabilitative practice of the rehabilitation center where the study was carried out, therefore, the normal ethics committee clearance was not required (19).

A total of 24 patients (12 males and 12 females, mean age 63 years) affected by COPD aggravated by fall AR were recruited. All patients presented clinical manifestations of dyspnea, cough, rhinorrhea and nasal congestion assessed by the medical doctors at the study site. Patients with severe cardiovascular diseases, neurological diseases and active infections were excluded from the study.

Patients were assessed, before the beginning (T0) and after the end (T1) of the CIT treatment cycle, using the following two COPD-specific rating scales:

- Medical Research Council dyspnea scale (MRC): a simple and valid method of categorizing patients with COPD and other respiratory diseases in terms of the influence of the respiratory deficit on their physical capacity (20). The scale measures the level of dyspnea perceived by the patient in a classification system divided into 5 levels of onset of breathing difficulties depending on the intensity of the activity performed (grade 0 = dyspnea after intense physical activity, grade 1 = dyspnea after walking at fast pace or uphill, grade 2 = dyspnea after walking at a slow pace on level ground, grade 3 = dyspnea after just 100 meters of walking, grade 4 = dyspnea when dressing/undressing) (20).

- COPD Assessment Test (CAT): used to evaluate the health status of patients with COPD and other respiratory diseases (21,22). Indeed, it contains items focused on respiratory symptoms and non-respiratory symptoms such as sleeping disturbance or limitations in activities at home. In particular, the rating scale is made up of 8 items that investigate various aspects related to the respiratory capacity of the patient, such as cough, mucus, chest tightness, physical resistance to walking, physical resistance to domestic activities, perceived safety in leaving the home environment, noise of the sleep and perceived energy level. Each item assesses the severity of the symptomatology with a score from 0 (no symptoms) to 5 (extremely present and disabling symptom) (21,22).

The CIT protocol applied in the study consists of the administration of the following respiratory stimulation techniques:

- Inhalations: steam inhalations with direct warm humid jets placed in front of the face of the patient. The jets are carried out through proprietary individual devices from which the bicarbonate-sulphate-alkaline-earthy mineral water comes out from a nozzle in the form of a homogeneous mist at a pressure of 1.5 atmospheres and at a temperature of 37°C-38°C, lasting about 20 minutes. This phase of the CIT treatment is dedicated to the stimulation of the very upper airways.
- Aerosol: it applies the same jet as the inhalation phase but focused through a nose-mouth mask directed only to the respiratory tract, integrating a system of micronization of the bicarbonate-sulphate-alkaline-earthy mineral water vapor jets, lasting around 20 minutes. This phase is dedicated to a deeper stimulation of the upper respiratory tract.
- Noninvasive mechanical ventilation: produced through a Bird Mark 8 instrumentation (Bird Products 3M, Palm Springs, California, U.S.A.). The treatment, consisting of ad-ministering pressurized purified air to the patient through the use of a positive pressure mouthpiece, was applied with an automatic frequency of no more than 14 breaths per minute (according to specialist medical indication) for a total of 15 minutes. This phase aims to stimulate the respiratory system at depth, involving also direct pulmonary involvement.

Each patient underwent 6 weekly sessions of CIT for 2 weeks, for a total of 12 treatment sessions lasting around 1 hour each.

At the end of the study, statistical analysis was carried out on collected data using the Wilcoxon Signed Rank test for dependent samples, performed through the Statistics Kingdom online calculator (https://www.statskingdom.com, Melbourne, Australia).

RESULTS

At the end of the study (T1), a significant reduction in the MRC score value was observed ($p < 0.001$) which went from 1.54 ± 0.88 to 0.83 ± 0.64, for an overall reduction of 45.9% (Fig.1).

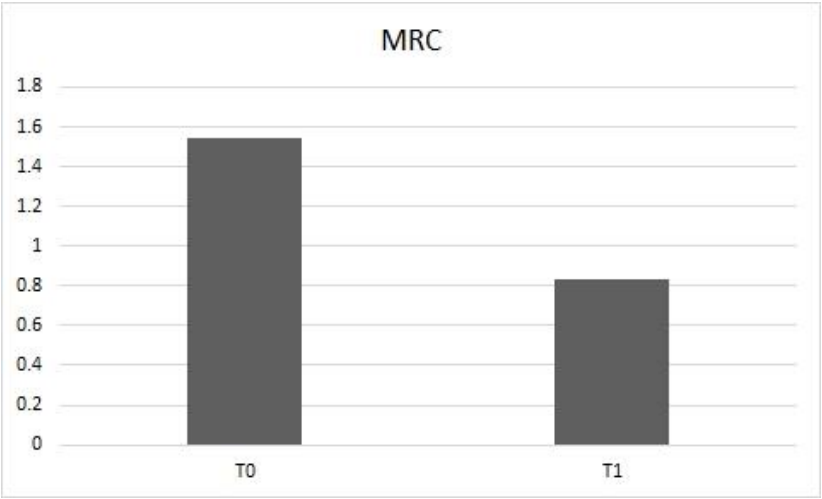

Fig. 1. *Change in MRC values between T0 and T1.*

Similarly, at time T1, a significant reduction in the CAT value was observed ($p < 0.001$) which went from 17.83 ± 7.47 to 9.29 ± 5.01, for an overall reduction of 47.9% (Fig.2).

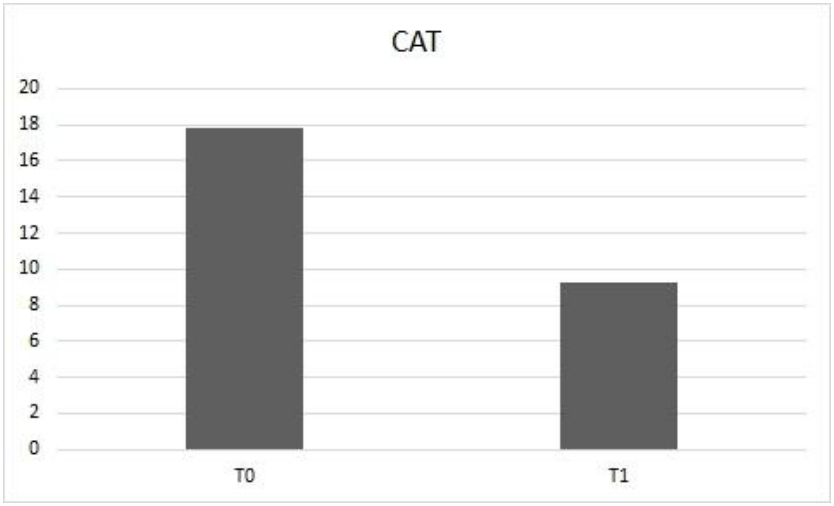

Fig. 2. *Change in CAT values between T0 and T1.*

DISCUSSION

The application of a CIT protocol in the group of patients selected for the study significantly reduced, after 2 weeks of treatment, both the MRC and CAT scores in the presence of COPD aggravated by AR.

Current literature suggests that AR is a pathological condition frequently associated with chronic respiratory diseases such as asthma (23,24); however, a growing body of evidence is now demonstrating that the nasal and upper respiratory tract symptoms typical of AR and other forms of rhinitis could have a strong pathological influence even in association with the presence of COPD (25,26). This could be due primarily to a mutually exacerbating and cumulating effect of the inflammatory and possibly infectious processes that characterize both the upper and lower respiratory tract, as in the case of AR associated with COPD (26,27). Furthermore, it is assumed that nasal affections, such as AR, have a direct influence on the reduction of respiratory flow already compromised downstream in the presence of COPD (28). In fact, nasal obstructions due to rhinitis contribute markedly to the reduced airflow in COPD patients, to the point of allowing the identification of pan-airway involvement in COPD (28). By virtue of this, clinical practice could benefit from the treatment of upper respiratory tract symptoms, such as nasal symptoms of AR, in the presence of COPD, in order to also bring improvements to the latter condition (26). Typically, this is done through drug therapies which have been shown to be effective in improving the quality of life of COPD patients through treatment dedicated to nasal symptoms (29,30).

What has been observed so far would appear to be consistent with the improvements observed in terms of MRC and CAT scores in COPD+AR patients treated in our study through a 2-week CIT cycle. The fact that both scores showed improvement with the CIT approach reinforces the idea discussed so far that therapy dedicated to upper respiratory tract conditions, such as fall AR, is able to produce benefits that are directly reflected also on COPD-induced respiratory dysfunction. This is particularly relevant if we consider that, in addition to a significant reduction between T0 and T1, both the mean MRC and CAT values detected at the end of the CIT protocol fell below the scores pathological cut-off typically recognized in the literature, corresponding to ≥2 for MRC and ≥10 for CAT (31). The positive effects of the CIT treatment are most likely attributable to the well-known anti-inflammatory and decongestant effects of thermal mineral waters, particularly of the sulfurous type, which are especially evident in the upper respiratory tract and nasal mucosa (32,33). The anti-inflammatory effect of thermal mineral waters on the upper respiratory tract was also confirmed for the bicarbonate-sulphate-alkaline-earthy mineral water used for the first two phases of the CIT protocol administered to the study patients (34).

Despite the broad consistency of the results obtained with what is known in the literature regarding the curative potential of thermal mineral waters and the efficacy of CIT protocols in conditions such as AR and COPD, it is necessary to underline some limitations of this study. First of all, the observed sample is relatively small compared to the wide diffusion that AR and COPD have in the general population: this is due to the selection methods of the subjects studied, who were taken from users who typically turn to the study center for recreational spa treatments (35), without resorting to targeted and organized recruitment a priori. Furthermore, the study, for the same reasons mentioned above, did not include a control group or a follow-up. Therefore, given the excellent results obtained, in order to clearly validate the efficacy of CIT for patients affected by COPD aggravated by AR, it would be appropriate to make new studies on the topic, larger and better structured, possibly with a control group and follow-up. It would also be important to take into consideration, for any new studies on the topic, the use of biochemical markers and instrumental and laboratory analyses

among the evaluation methods, so as to have a clearer picture of the actual existence of anti-inflammatory mechanisms underlying the therapeutic effects of CIT.

CONCLUSIONS

The CIT approach can determine a significant improvement, at least in the short term, of MRC and CAT parameters of patients affected by COPD aggravated by AR. Given the non-invasiveness of the treatment and the relatively simple and safe application of the studied protocol, this method could be configured as a complementary or alternative therapeutic tool in the rehabilitation of complex and widespread respiratory disorders such as COPD and AR.

Conflict of interest

The authors declare that they have no conflict of interest.

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INFECTIONS FOLLOWING HEART SURGERY

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ABSTRACT

Postoperative infections, including those that affect the heart, can be very serious and complex and prolong hospital stay and recovery. Infection with microorganisms can occur through the contamination of surgical instruments or through other routes of microbial entry. Surgical infections can be superficial or severe, as occurs in endocarditis. Severe or deep mediastinal infections may involve the sternum and cause fever and pain. These infections can be treated with either surgery or antibiotics. Sepsis is a serious infection that occurs when bacteria enter the bloodstream and causes rapid heart rate and breathing, and in some cases, death. Postoperative infection involves complex biochemical and biological mechanisms. Pathogen-associated molecular patterns (PAMPs) are recognized by pattern recognition receptors (PRRs) located on immune cells such as macrophages and dendritic cells. The immune reaction leads to the production of inflammatory cytokines and chemokines, with vasodilation and increased vascular permeability. Chemokines attract leukocytes such as neutrophils and monocytes to the site of infection. infections can occur after surgery where the pathogenic organism activates the immune system resulting in inflammation.

KEYWORDS: *Infection, heart surgery, postoperative, immune system, pathogen*

INTRODUCTION

Postoperative infection involves complex biochemical and biological mechanisms and may be a serious complication (1). Infections of the heart can lead to delayed recovery, prolonged hospital stay, and in severe cases, can be life-threatening (2). During surgery, pathogens, such as bacteria, viruses, fungi, or other microorganisms, can enter the body through the incision and activate immune cells that cause inflammation (3). Contamination can occur through the patient's skin, surgical instruments, the air, or the hands of the surgical team (4). Factors that may influence susceptibility to postoperative infection include the patient's age, immune status, and the presence of comorbidities (such as diabetes).

Postoperative infections can be located anywhere in the body and vary in severity. Infections can be superficial, involving the skin, with burning, heat, and pain, but they can also be internal, involving the lining of the heart, such as the heart valves. The common types of heart infections are superficial wound infections, mediastinitis, and endocarditis (5). Superficial infections mainly involve the skin and the area around the surgical site, with the classic symptoms of inflammation: "*calor*, *rubor*, *tumor*, *dolor*, and *fuctio laesa*". Mediastinitis is inflammation in the mediastinum which contains the heart, large blood vessels, esophagus, trachea, thymus gland, lymph nodes, and connective tissue. Endocarditis is inflammation that occurs in the inner lining of the heart's chambers and valves, which can be severe and life-threatening.

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DISCUSSION

Infection involves a series of complex biochemical and biological mechanisms that occur as the body attempts to protect itself from invading microorganisms, which first activate the innate immune system, the first line of defence of the body (6).

Pathogen-associated molecular patterns (PAMPs) on the surface of microbes are recognized by pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) on immune cells. Recognition of PAMPs leads to the activation of immune cells, such as macrophages and dendritic cells, which release cytokines and chemokines to recruit more immune cells to the site of infection (7). This results in the release of cytokines and chemokines, causing vasodilation, increased vascular permeability, and the recruitment of neutrophils and other leukocytes to the site of infection (7,8).

Neutrophils are first responders and play a critical role in the phagocytosis of pathogens, engulfing and digesting pathogens, and the release of antimicrobial substances. Immune cells also produce reactive oxygen species (ROS) and nitric oxide (NO) (9). Peptides are released by immune cells and epithelial cells and have antimicrobial properties that help kill and degrade pathogens.

In the adaptive response to pathogens, dendritic cells and macrophages present antigens to helper and cytotoxic T cells, initiating the immune response. B cells are also activated to produce antibodies against pathogen antigens (10). The adaptive immune system forms memory cells that provide long-lasting protection against future infections by the same pathogen.

Microbes activate nuclear factor-kappa B (NF-κB), a transcription factor activated by PRRs (11). NF-kB plays an important role in the expression of pro-inflammatory cytokines. The complement system is a series of activated proteins that enhance phagocytosis, lyse bacteria, and mediate inflammation, which also plays a role in the immune response. In postoperative infections, matrix metalloproteinases (MMPs) are involved in tissue remodelling and repair but can also contribute to tissue damage (12).

Microorganisms evade the immune response through various strategies, including the formation of biofilms on surgical implants which protect them from immune cells and antibiotics (13). In addition, bacteria defend themselves from the immune system by producing factors that inhibit complement activation and phagocytosis or alter antigen presentation (14).

In surgical infections, the site of infection must be monitored continuously, and blood tests and cultures should be performed to identify and control systemic infections. If the infection is deep, a chest x-ray or CT scan is performed (15). Follow-up with the surgical team and infectious disease specialists is also crucial.

Superficial infections are treated with wound cleaning and topical antibiotics, or oral antibiotics if necessary (16). In deep mediastinal infections, the sternum may also be involved and there may be fever and pain (17); these infections are treated surgically with removal of the infected tissue, or with intravenous antibiotics. In endocarditis involving the inner lining of the heart, particularly the heart valves, symptoms include fever, heart murmur, night sweats, chills, and fatigue (2). Treatment for endocarditis consists of long-term use of antibiotics, or surgery which may be needed to repair or replace infected heart valves (2).

Internal heart infections can cause fever, fatigue, and a heart murmur. Systemic infections caused by bacteria entering the bloodstream can cause sepsis infection with low blood pressure, fever, rapid heartbeat and breathing, and confusion. Sepsis is a severe condition that can be life-threatening if left untreated. Certain individuals are at higher risk of developing this type of infection, and the duration of surgery, type of surgery, and use of implants or prostheses may also increase the risk of infection (18) (Table I).

Table I. *Risk factors for the development of sepsis infection.*

Patient risk factors	*Surgical risk factors*
• Diabetes	• General surgical factors
• Advanced age	• Prolonged surgery duration
• Obesity	• Use of extracorporeal circulation (heart-lung machine)
• Immunocompromised state (e.g., due to medications or conditions)	• Reoperation
• History of smoking	• Improper surgical technique
• Poor nutritional status	

Treatment of sepsis should be done immediately by administering broad-spectrum IV antibiotics, with supportive care in an intensive care unit (ICU), including fluids, vasopressors, and organ support. Preoperative measures, including the use of antibiotics and proper preparation, execution, and care of the surgical site, are of the upmost importance to avoid the risk of infection (19) (Table II).

Table II. *Surgical measures that lower the risk of sepsis.*

• Use of prophylactic antibiotics.	• Early removal of invasive devices (e.g., catheters, drains).
• Proper antiseptic preparation of the surgical site.	• Proper wound care and hygiene.
• Sterile surgical techniques.	• Monitoring for early signs of infection.
• Minimizing the duration of surgery and use of invasive devices.	• Continued use of prophylactic antibiotics as appropriate

CONCLUSIONS

Infections can occur after surgery with a complex dynamic involving the host immune system and the pathogen. Understanding these mechanisms could lead to better pharmacological antibiotic and surgical therapy. However, infections can be effectively managed with early diagnosis and appropriate treatment. Accurate prevention significantly reduces the incidence of infections and rigorous preoperative, intraoperative, and postoperative strategies are important to minimize the risk and impact.

Conflict of interest

The authors declare that they have no conflict of interest.

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Letter to the Editor

RETROPHARYNGEAL ABSCESS IS A SERIOUS INFECTION THAT DESERVES ATTENTION

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KEYWORDS: *Retropharyngeal abscess, retropharyngeal space, infection, bacteria, inflammation*

INTRODUCTION

Retropharyngeal abscess (RPA) is a serious, life-threatening infection that affects the area behind the pharynx called the retropharyngeal space (1). This infection occurs primarily in children but can also affect adults. RPA is caused by bacterial infection which leads to swelling, inflammation, the accumulation of pus, and obstruction of the airways. In primary infection, the retropharyngeal space may become infected by nearby structures that include the paranasal sinuses, pharynx, tonsils, teeth, and middle ear (2). Upper respiratory tract infections, such as pharyngitis or tonsillitis, often precede the development of RPA. In some cases, bacteria can enter the retropharyngeal space and infect the lymph nodes, causing tissue trauma, inflammation, and pain. In children, more than in adults, these infections can form abscesses that often regress with age. In the infected area, bacteria multiply and generate pus in the retropharyngeal space and cause inflammation.

DISCUSSION

The immune reaction to RPA is orchestrated by immune cells including neutrophils, macrophages, and later, lymphocytes, which release enzymes and reactive oxygen species (ROS). These are necessary molecules to combat microorganisms, even though they often cause tissue damage (3).

The pus that forms in the abscess is a pocket of infected fluid surrounded by inflamed tissue. If the abscess enlarges, it can push against the posterior wall of the pharynx, potentially leading to airway obstruction, dysphagia, and difficulty in breathing. RPA is mostly caused by group A *Streptococcus pyogenes*, *Staphylococcus aureus*, and anaerobic bacteria, but in some cases, *Haemophilus influenzae* may also be involved.

As in other bacterial infections, the first line of defense includes the activation of neutrophils and macrophages. These cells recognize pathogen-associated molecular patterns (PAMPs) via pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs). In adaptive immunity, the immune system becomes involved with the activation of T-cells, B-cells, and their subsets, leading to antibody production and a more specific immune response. In innate immunity, pro-inflammatory cytokines such as IL-1, IL-6, and TNF are released, which recruit more immune cells to the site of infection (4).

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S. pyogenes produces toxins and enzymes, such as streptolysins and hyaluronidase, that contribute to the spread of infection and tissue damage. In an attempt to destroy the bacteria, activated neutrophils release myeloperoxidase and elastase, although these enzymes also contribute to tissue damage.

The abscess environment is hypoxic, which can affect the survival and virulence of some bacteria, especially anaerobic bacteria. The formation of a fibrous capsule around the abscess by fibroblasts can limit the spread of infection and compromise immune access, making it difficult for antibiotics to penetrate and effectively treat the abscess (5).

Diagnostic identification of an RPA can be made using imaging techniques such as CT scans. Treatment is performed with antibiotics, which cover both aerobic and anaerobic bacteria, and the abscess may require surgical drainage if it is large or if there is a risk of airway compromise.

CONCLUSIONS

In conclusion, RPA is a serious infection that results from bacterial infiltration of the retropharyngeal space, leading to the formation of an abscess. The reactions that occur between virulent bacteria and the host's immune response are quite complex and it is necessary to treat RPA promptly to avoid serious and significant risks.

Conflict of interest

The author declares that they have no conflict of interest.

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THE MOLECULAR MECHANISMS OF TOXOPLASMA GONDII, A PROTOZOAN THREAT TO HUMAN HEALTH

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ABSTRACT

Toxoplasmosis is an infection caused by the *Toxoplasma gondii* parasite which can lead to serious complications in immunocompromised individuals and during pregnancy. The relationship between *T. gondii*, immunity, and inflammation is complex and infection depends on the host's immune response and the parasite's ability to evade immune defenses. *T. gondii* is usually transmitted to humans by ingestion cysts, directly from mother to fetus during pregnancy, or through organ transplantation or blood transfusion. *T. gondii* induces a strong innate and adaptive immune response with the activation of macrophages and T and B cells, respectively. *T. gondii* secretes proteins from micronemes (MICs) and rhoptries, and these proteins facilitate cell attachment, entry, and the formation of vacuole parasitopophore. MIC2 and MIC6, interact with the surface membrane of host cells to start the invasion, while the rhoptry proteins (ROPs) are injected into the host cytoplasm. The dense granules proteins of the parasite, such as GRA15 and GRA24, are secreted into the host cell to modulate the inflammatory responses. *T. gondii* uses lipids for cell membrane synthesis and replication and tryptophan from the host cell for its vital growth. In this article, the biochemical and mechanical mechanisms of action of *T. gondii* in the host cell and the immune and inflammatory responses it induces are discussed.

KEYWORDS: *Toxoplasma gondii, protozoa, parasite, toxoplasmosis, infection, immunity*

INTRODUCTION

Protozoa are single-celled eukaryotic organisms that live in a variety of environments, including soil, water, and inside other organisms (1). Some protozoa are parasites that live at the expense of their host, causing disease in humans and animals (2) Among the most well-known protozoan parasites is *T. gondii*, which is an intracellular protozoan that infects the host through the oral route (3). This parasite can infect a variety of animal species, including mammals, and causes the disease toxoplasmosis, which can be asymptomatic, but can also be severe or potentially fatal if it affects immunosuppressed individuals or during pregnancy (4).

T. gondii can be found as undeveloped and/or developed oocysts, and cysts. This parasite prefers to reproduce in cats; however, it can infect many different animals, including humans. Toxoplasmosis is often transmitted through contact with infected cat feces or undercooked meat.

In healthy people, toxoplasmosis is often asymptomatic but can be serious for pregnant women or immunocompromised individuals. During pregnancy in women who are infected with *T. gondii* for the first time, the parasite can cross the placenta and infect the fetus, which has the potential to cause congenital toxoplasmosis that may

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produce serious developmental problems or miscarriage (5). Additionally, infection may cause neurological or ocular damage to the fetus.

The pathogenesis of this ubiquitous disease is still quite obscure, and it is important to clarify it given that it afflicts both industrialized and non-industrialized countries. The parasite's ability to establish a latent infection and evade immune responses still presents a challenge to overcome.

DISCUSSION

The pathogenic process of *T. gondii* which leads to infection and dissemination within the host occurs in several stages (6). *T. gondii* is usually transmitted to humans through ingestion of tissue cysts from undercooked meat or water contaminated with oocysts, through direct transmission from mother to fetus during pregnancy, or by organ transplantation or blood transfusion.

After ingestion, the parasite passes through the stomach and reaches the intestine, where sporozoites or bradyzoites are released from cysts (7). These forms differentiate into tachyzoites, which replicate rapidly and are responsible for acute infection. Tachyzoites invade host cells, particularly macrophages, fibroblasts, neurons, and muscle cells, by actively penetrating the plasma membrane. During active invasion, *T. gondii* enters host cells through a specialized process known as gliding motility (8). The parasite's actin-myosin motor complex drives this process, allowing it to rapidly invade cells without damaging the host membrane (9).

In humans, toxoplasmosis can initially cause mild flu-like symptoms and psychiatric disorders, including bipolar disorder (10). In immunocompromised individuals, *T. gondii* primarily affects the central nervous system (CNS) and can be lethal (11). Live but non-activated cysts (controlled by the immune system) that form within muscles and neurons can remain in the host throughout their entire lifespan.

The life cycle of *T. gondii* has a sexual component in the non-domestic cat and an asexual component that can occur in all warm-blooded animals, including humans (12). The definitive host of *T. gondii* is the cat, where it reproduces, while all other animals are intermediate hosts where only asexual reproduction can occur.

The surface of *T. gondii* includes a family of proteins regulated by glycosylphosphatidylinositol (GPI)-linked proteins (SRS) of which SAG1 (P30) is the prototypical member (13). *T. gondii* cysts develop in muscles, neurons, and other tissues and infect intermediate host animals which go on to infect the definitive host animal. The intermediate hosts include many species (over 200) such as horses, pigs, dogs, rabbits, and rats.

T. gondii infection typically occurs when a cat ingests an infected mouse containing the cysts of the parasite, which pass through the stomach and infect the epithelial cells of the animal's intestine (14). In intestinal cells, parasites undergo sexual reproduction and produce millions of walled cysts containing zygotes called oocysts. The cat is the definitive host as, not having the delta-6-desaturase enzyme in the intestine, it cannot convert linoleic acid which is important for the sexual reproduction of *T. gondii* (15). Infected epithelial cells eventually rupture and release oocysts into the intestine which shed in the feces. Oocysts can survive in soil at very cold temperatures and cause infection if they are eaten by humans and other animals, which in turn become intermediate hosts (12). Cysts containing sporozoans are released inside the animal and the sporozoans implant into the muscles where they form adult cysts (16).

The immune response to *T. gondii* is robust and involves both innate and adaptive mechanisms. This can have significant impacts on human health, especially in immunocompromised individuals or pregnant women (17). Individuals with weakened immunity are at increased risk of severe toxoplasmosis or reactivation, as the immune system may not be able to suppress latent stages of the parasite.

At the beginning of *T. gondii* infection, innate immune cells are activated, such as macrophages and T cells which produce IL-2 and interferon-gamma (IFN-γ). T cells such as CD4+ and CD8+ play an important role in immunity against toxoplasmosis (17). Major histocompatibility complex (MHC) presents *T. gondii* antigens to T cells, which determines the severity of the infection (18). CD4+ T cells are essential for orchestrating the immune response, secreting cytokines like IFN-γ and helping to maintain control over chronic infection (19). CD8+ T cells are cytotoxic T cells which recognize infected cells and kill them to limit the spread of the parasite. They also produce IFN-γ, which further enhances immune defenses (20).

IFN-γ is a cytokine that is very important in the immune defense against *T. gondii*. It activates macrophages to produce reactive nitrogen and oxygen species, which can kill the parasite inside cells. IFN-γ also stimulates the production of indoleamine 2,3-dioxygenase (IDO), an enzyme that deprives *T. gondii* of tryptophan, a vital nutrient for its survival (21). B cells produce antibodies (IgG and IgM) specific to *T. gondii*. These antibodies help neutralize extracellular parasites and mark them for destruction by immune cells like macrophages (22).

The pathogenic effect of *T. gondii* is carried out in different phases with the diffusion and infection of the host. The transmission of the parasite can occur through different mechanisms, such as ingestion of cysts with raw or undercooked

meat, or with contaminated water. Toxoplasmosis can also be congenital when it happens during pregnancy with fetal transmission from the mother (6). In addition, infection can occur in the event of blood transfusion or organ transplantation (23).

After the ingestion, the parasite passes through the stomach and reaches the intestine, where sporozoites or bradyzoites from the cysts are released. These are different forms of tachizoites that invade host cells such as macrophages, fibroblasts, muscle cells, and neurons. The parasite's actin-myosin motor complex allows it to quickly invade the cells. After invasion, *T. gondii* lies in a vacuole parasitophore that derives from the guest cell membrane but is modified by the parasite to avoid melting with lysosomes and subsequent degradation (24). The parasite replicates inside the cell and releases tachizoites which infect new cells.

The infection spreads throughout the body through the blood and lymphatic system, arriving to the brain and muscles, where chronic cysts are formed. At this point, the tachizoites differ into bradyzoites, which persist in tissue cysts (particularly in muscle and neural tissues) and lead to chronic infections (25). The cysts demonstrate a useful process in immunosuppression by escaping the immune system while also activating it.

T. gondii release proteins from specialized secretory organelles called micronemes (MICs) and rhoptries (18). These proteins facilitate cell attachment, entry, and formation of vacuole parasitopophores. MICs, such as MIC2 and MIC6, interact with the surface membrane of the host cells to initiate the invasion, while the rhoptries are injected into the host cytoplasm, where the reporting routes of the host cells manipulate, modulate immune responses, and promote survival (26). The kinases ROP18 and ROP5 interfere with the immuno-related GTPasi of the host which causes the interruption of the vacuole parasitophore (27). By interrupting these mechanisms, the host cell is unable to attack the parasite.

The parasitic dense granule proteins, such as GRA15 and GRA24, are secreted into the host cell to modulate inflammatory responses, including the alteration of the NF-kB signaling routes and MAPK with disruption of the host's immune response, for the benefit of the survival of the parasite (28).

T. gondii has efficient systems to obtain essential amino acids from the host, such as tryptophan, which is vital for parasitic growth. Host cells often deplete tryptophan as an immune defense (29). *T. gondii* uses host lipids, for cell membrane synthesis and replication. The parasite can modulate host lipid metabolism by altering key pathways involved in fatty acid and sterol synthesis.

T. gondii also employs glycolysis, which is crucial for its survival and replication, and for maintaining chronic infection (30). Glycolysis is essential during the tachyzoite phase, where rapid energy demands are met by breaking down glucose into pyruvate. During chronic infection, bradyzoites switch to more efficient oxidative phosphorylation to conserve energy. Additionally, *T. gondii* relies on *de novo* fatty acid synthesis for membrane production during its replication phase. It uses a unique type II fatty acid synthesis (FAS II) pathway that is different from that found in humans, making it a potential drug target (31).

Other biochemical pathways include the methylerythritol phosphate (MEP) pathway in the apicoplast, which is responsible for the synthesis of isoprenoid precursors that are essential for cellular functions such as membrane maintenance and protein prenylation (32). The apicoplast also plays a role in the FAS II pathway, which is crucial for the synthesis of fatty acids used in membrane generation.

T. gondii can utilize various nutrients from its host, including purines and lipids. The parasite does not have the ability to synthesize purines *de novo*, so it relies on scavenging them from the host cell for DNA and RNA synthesis (33). Furthermore, *T. gondii* has sophisticated transporters to take up amino acids from the host. Arginine metabolism is particularly important, as arginine deprivation can suppress the host immune response by limiting nitric oxide production (34).

CONCLUSIONS

Toxoplasmosis is caused by infection with the *T. gondii* protozoan. It is a parasitic infection that can lead to serious complications in immuno-compromised individuals and during pregnancy *T. gondii* elicits an innate immune response that activates TH1 and TH2 cells. Macrophages and cytotoxic T cells produce inflammatory cytokines and generate IFN-γ, which are essential for controlling the infection. Inflammation is a key factor in the pathogenesis of toxoplasmosis, with a balance required between effective parasitic control and limiting tissue damage.

The interaction of the parasite with the host leads to complex molecular and biochemical mechanisms, as well as immune evasion strategies that allow the parasite to survive. Prevention of *T. gondii* infections is mainly based on hygienic measures, such as avoiding contaminated water, cooking food properly, taking preventive measures during pregnancy, and, in some regions, employing protection from insect bites. Treatment usually involves the use of *T. gondii*-specific antiparasitic drugs.

Research on human vaccines is ongoing, and therefore, no approved human vaccine against *T. gondii* exists as to date. Studies are also focusing on vaccines that enhance T cell and IFN-γ-mediated responses, which are central to strengthen the immune response against the parasite. Future studies on these topics should continue to shed light on the parasite-host reaction and immune and inflammatory activation.

Conflict of interest

The authors declare that they have no conflict of interest.

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COUGH TRIGGERED BY VIRAL INFECTION

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ABSTRACT

Cough is a reflex mechanism that is common in many infections, especially those affecting the respiratory tract. Cough is a nociceptive reflex that can be caused by viral infections, such as colds or the flu. Bacteria can also be a cause of cough, as occurs in pneumonia or bacterial bronchitis. Cough can develop as dry cough (caused by viral infections), productive cough with phlegm (typical of bronchitis and pneumonia), and persistent cough due to prolonged inflammation. Cough receptors are divided into mechanoreceptors which are sensitive to mechanical stimuli such as bronchospasm, edema, mucus, and foreign bodies, and chemoreceptors which are mainly sensitive to chemical stimuli including inflammatory cytokines, gases, and smoke. Both mechanoreceptors and chemoreceptors bind irritants of the myelin type, and they are sensitive to capsaicin. Respiratory syncytial virus (RSV) is a virus that affects the respiratory system and causes a persistent cough that can range from mild to severe. RSV primarily infects the lungs and airways, where it causes inflammation of the bronchioles and stimulates mucus production. The cough may cause serious symptoms such as high fever, bluish skin due to low oxygen levels, and short or long apnea. Various agents can cause cough by activating molecular and biochemical mechanisms, including viruses which can activate the immune and inflammatory response with the irritation of the airways and nerve stimulation.

KEYWORDS: *Cough, virus, infection, receptor, bronchiolitis, respiratory syncytial virus*

INTRODUCTION

Cough is a nociceptive reflex mechanism controlled by the brain stem in the "cough center" in response to sensory afferent stimuli. Motor efferent stimuli produce cough by forced expectoration with a closed glottis (1). Cough aims to remove noxa that accidentally encounters the respiratory tree (2). It is one of the most important defence mechanisms of the body and has been referred to as the "watchdog of the respiratory system" (3).

The cough reflex is stimulated by receptors that are sensitive to foreign substances such as infectious, mechanical, and chemical stimuli. These receptors are present in the epithelium of the main airways, the posterior part of the trachea, the pharynx, cornea, the proximal airways, the paranasal sinuses, the stomach, the external auditory canal, the pleura, and the pericardium; they are absent in the alveoli (Fig.1).

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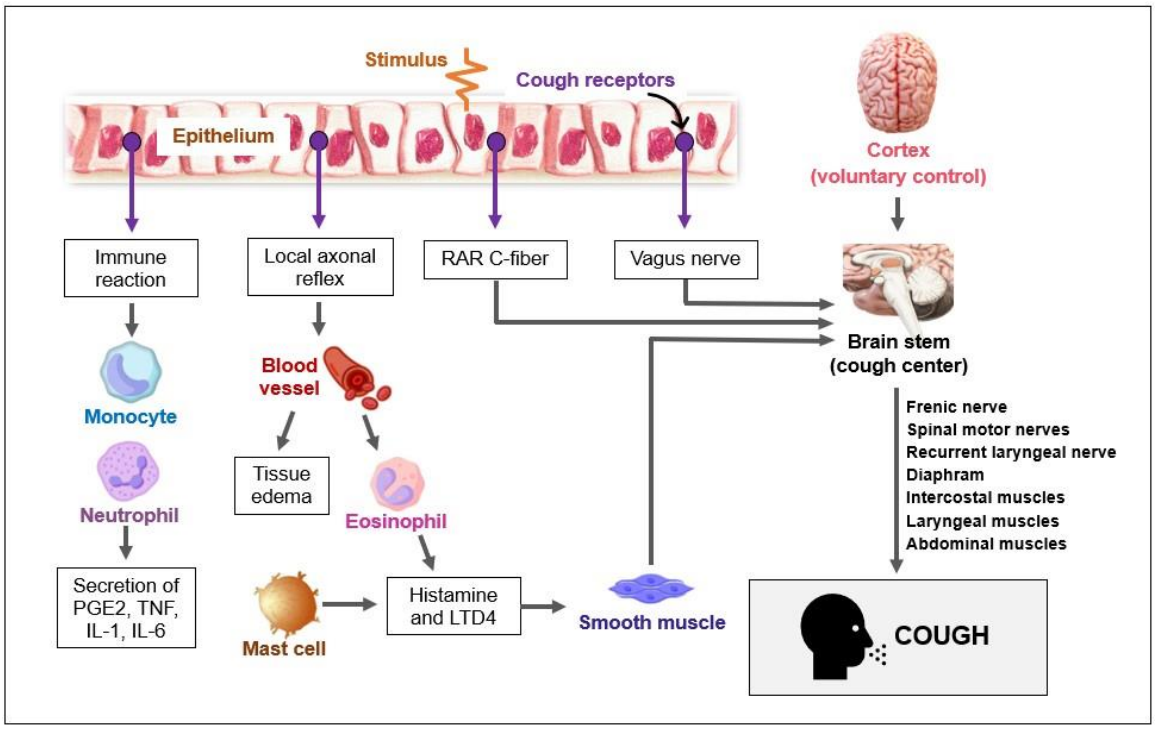

Fig. 1. *Cough receptors are activated in response to infectious, mechanical, and chemical stimuli, and cause an immune reaction that results in the secretion of inflammatory substances and a local axonal reflex that results in tissue edema and the release of histamine and LTD4 which affects smooth muscle cells to produce cough. Cough receptors also stimulate RAR C-fibers and the vagus nerve which participate in the activation of cough through the brain stem.*

Cough receptors include mechanoreceptors that are sensitive to mechanical stimuli such as bronchospasm, edema, mucus, foreign bodies, and chemoreceptors that are mainly sensitive to chemical stimuli including inflammatory cytokines, gases, and smoke (4). The density of mechanoreceptors is highest in the proximal walls of the airways such as the larynx and trachea. Chemoreceptors, on the other hand, are located primarily at the base of the airways (5). Receptors can be further divided into rapidly and slowly adapting irritant receptors of the myelin type, which includes both mechanoreceptors and chemoreceptors, and receptors sensitive to capsaicin which only include chemoreceptors (6). The latter are in the trachea and bronchi and are able to cause muscle contraction, vasodilation, and mucus secretion through an accentuation of the cough reflex.

Some individuals have a higher distribution of chemoreceptors, particularly capsaicin-sensitive receptors (7). These individuals have a greater frequency and duration of coughing episodes.

Once activated, cough receptors transmit impulses from the branches of the internal laryngeal nerve to the superior laryngeal and vagus nerves (8). Some afferents are transmitted through the glossopharyngeal and trigeminal nerves.

DISCUSSION

Cough is defined as chronic when it last for more than three weeks, and as acute when it lasts less than three weeks weeks (9,10). It is generally caused by viral infections and sometimes, accompanied by fever (11). The incidence of acute cough is high in the first years of life, especially in school-aged children, who can contract up to 6-8 viral infections of the upper respiratory tract each year.

Cough is characterized by sudden, intense, and annoying attacks, with the emission of mucus (12). In most cases of acute cough, a careful anamnesis and physical examination are sufficient for the diagnosis. Since most acute cough episodes have a viral etiology, specific therapy is almost never necessary (13). Cleaning the nasal cavities with saline solution and maintaining a raised decubitus during sleep are useful.

The areas of the central nervous system (CNS) responsible for controlling the cough reflex are in the brainstem (14). The efferent neural pathway starts from the cerebral cortex, passes through the nuclei of the brainstem tract, continues with the vagus nerve, the superior laryngeal nerve to the glottis, and is transmitted to the external intercostal respiratory muscles and diaphragm. Through the capsoid-sensitive C-fibers, the cough reflex is linked to the production of mucus in the submucosal glands and goblet cells, contributing to the establishment of a further defence mechanism,

since the action of the mucociliary clearance contributes to the removal of foreign substances from the mucosa of the respiratory tract (15).

Coughing is regulated by a complex muscular mechanism that can be divided into three phases. The first, called the inspiratory phase, involves the massive entry of air into the lung parenchyma (16). The diaphragm and the external intercostal muscles contract, creating a negative intrapulmonary pressure, which allows, together with the contraction of the abductor muscles of the arytenoid cartilages, the forced inspiration of air. The second phase, called the compressive phase, entails the closure of the glottis for about 2 tenths of a second (17). At the same time, there is a strong contraction of the abdominal muscles and the expiratory muscles, with an increase in air pressure inside the lungs up to 300 mm/Hg. The expulsive phase consists of the opening of the glottis, with the emission of air at more than 160 km/h (18). During a coughing fit, the compressive and expulsive phases can be repeated in succession, even without an inspiratory phase.

Chronic cough can be caused by various conditions that vary with the age of the patient. Cough may appear after an infection and is called post-infectious cough. This is caused by viral infections and is slow to resolve. The mechanism is related to persistent inflammation of the airways with transient hyperreactivity of cough receptors that continues after the elimination of the viruses (19). Cough can occur a few days after an episode of fever or concomitant with it and generally lasts from 3 to 8 weeks. An individual with post-infectious cough typically has a history of fever or cold episodes in the days preceding the cough. The specific infection causing the cough remains unknown in most cases. In the absence of a documented bacterial infection, there is no need for specific treatment. The recent guidelines of the American College of Chest Physicians recommend the use of inhaled ipratropium bromide as a supportive drug for the improvement of symptoms (20).

Viral infections can cause bronchiolitis, acute inflammation which is associated with bronchiolar obstruction and characterized by dyspnoea, tachypnoea, and wheezing (21). This is the most common lower airway disease in the pediatric population and is responsible for the majority of hospitalizations in the first twelve months of life. The diagnosis involves the use of classical and molecular diagnostic techniques and it has been shown that 97% of cases of bronchiolitis are of viral etiology, and that in 24% of cases of immunocompetent patients, more than one infectious agent is present (22). The main etiological agent is the respiratory syncytial virus (RSV), which is responsible for 45-75% of bronchiolitis cases in children, especially those that occur in epidemic form. Following RSV is metapneumovirus, parainfluenza virus types 1, 2, and 3, bocavirus, adenoviruses, and enteroviruses (23). More rarely, influenza viruses, echoviruses, rhinoviruses, or bacteria such as *Mycoplasma pneumoniae*, *Bordetella pertursis*, and *Simkania negevensis* are responsible.

Bronchiolitis is a highly contagious infection and is transmitted both by direct contact with nasal secretions of infected individuals and through direct contact by infected hands (21). The causative virus often survives at room temperature, for eight hours on the skin, and for about 6 hours on various surfaces. It is usually contracted in the community or through contact with an infected family member. Transmission occurs by elimination of the virus two days before the onset of symptoms and continues for about a week after their resolution. The virus prefers the winter months and early spring, sometimes manifesting itself with small epidemics in communities. According to estimates provided by the World Health Organization (WHO), 150 million new cases of bronchiolitis are observed each year around the world, of which 7-13% represent one of the categories at risk of developing severe forms which could require hospitalization (24).

RSV is a virus that affects the respiratory system, especially in young children and older adults (21). One of the hallmark symptoms of RSV is a persistent cough, which can range from mild to severe. RSV primarily infects the lungs and airways, causing inflammation of the bronchioles and stimulating the production and accumulation of mucus that causes coughing. Cough is a protective reflex to eliminate pathogens, including RSV, from the respiratory tract (25). Coughing can last for several weeks, even after other symptoms have subsided, and is often accompanied by mucus that is difficult to clear. Serious symptoms that can occur with a cough include high fever, bluish skin or lips due to low oxygen, and apnea with pauses in breathing that may be short or long (26). Treatments include hydration to help thin the mucus, saline drops or sprays, and bronchodilators which help open the airways. Most often, cough caused by RSV resolves spontaneously, but it is essential to monitor for any complications such as bronchiolitis or pneumonia.

CONCLUSIONS

In the airways, viral infections can cause cough by activating molecular and biochemical mechanisms. Cough involves a cascade of events that begin with the entry of the virus, activation of the immune response, and nerve stimulation. Coughing causes irritation of the airways, increased mucus production, and inflammation, and can lead to more severe symptoms such as high fever, low oxygen levels, and apnea.

Conflict of interest

The authors declare that they have no conflict of interest.

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MAPK IS IMPLICATED IN SEPSIS, IMMUNITY, AND INFLAMMATION

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ABSTRACT

The mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway is a chain of cellular proteins that communicate from the receptor to the cellular DNA. The receptor binds effector molecules and transmits the signal to the DNA that induces protein kinases and generates a protein. Protein kinases are produced by the cells themselves through the process of gene expression. Innate immunity and adaptive immunity are activated during infections with activation of the mitogen-activated protein kinase (MAPK) and receptor-interacting kinase (RIPK) pathways that regulate the balance between cell survival and death, as well as the production of pro-inflammatory molecules. In sepsis, this balance fails. Serine-threonine kinase, or kinase 1, is responsible for the activation of multiple MAPKs. MAPK activation appears in many cellular processes, including differentiation, proliferation, and apoptosis, and leads to activation of transcription proteins with production of inflammatory cytokines. MAPKs, which can be stimulated by cytokines and microorganisms, mediate extracellular signal-regulated kinases (ERKs) involved in cell growth and survival and c-Jum N-terminal kinases (JNKs) linked to apoptosis. These protein kinases are produced in all eukaryotic and prokaryotic cells and play a crucial role in signal transduction, cell cycle regulation, and many other biological processes.

KEYWORDS: *MAPK, pathway, sepsis, immunity, inflammation, cell signaling, receptor*

INTRODUCTION

The Ras-Raf-MEK-ERK pathway, also known as the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway, is a chain of cellular proteins that communicate a signal from a receptor on the cell surface to the DNA in the cell nucleus (1). The signaling molecule binds to the cell receptor to initiate the signal which results in the DNA in the nucleus expressing a protein to cause a change in the cell, such as cell division and metabolism, for example (2).

The MAPK/ERK pathway includes many proteins, such as mitogen-activated protein kinases (MAPKs). MAPKs communicate by adding phosphate groups to a neighboring protein (phosphorylating it), thus acting as an "on" or "off" switch. The immune system uses various signaling pathways to defend itself from infections. Both nonspecific, innate immunity and specific, long-term adaptive immunity are activated during infections. Once the immune system is activated by infection, pathways such as MAPK and receptor interacting protein kinase (RIPK) are also activated (3). These pathways orchestrate the balance between cell survival, cell death, and the production of pro-inflammatory molecules (4).

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Sepsis occurs when this balance fails, and the body's immune response becomes overwhelming. Both excessive activation of MAPK-driven cytokine release and RIPK-mediated cell death can drive the uncontrolled inflammation and organ damage that characterize sepsis (5).

Serine-threonine kinase, or kinase 1, is ubiquitous in cells and is responsible for activating multiple MAPKs to regulate biological processes, including infections (6). Activation of MAPKs leads to downstream signaling and activation of transcription proteins with the production of inflammatory cytokines (7) (Fig.1). MAPK signaling and integrins play an important role in microbial-induced infections. MAPK activation occurs in many cellular processes, including differentiation, proliferation, apoptosis, and both innate and adaptive immune responses, and MAPK stimulators include both cytokines and microorganisms (8). MAPK mediates various cellular pathways, such as ERKs that are involved in cell growth and survival, and c-Jum N-terminal kinases (JNKs) that are associated with apoptosis and pathogen-induced inflammatory responses (9). When cells are infected by pathogens, MAPK pathways are activated to defend the host from infection, and this creates an inflammatory response.

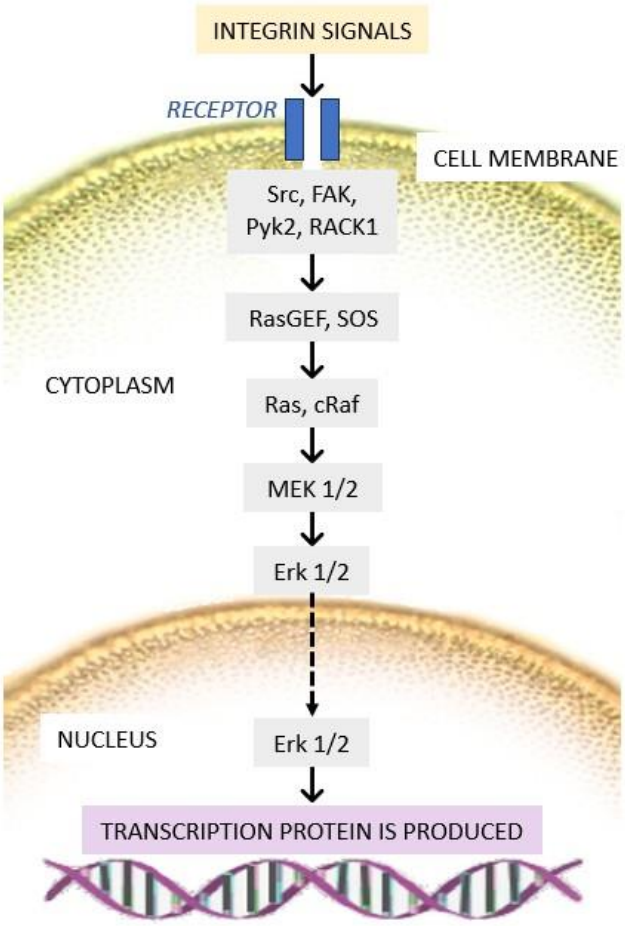

Fig. 1. *Integrin signaling on the cell cytoplasmic receptor leads to the activation of a nuclear transcription protein cascade.*

DISCUSSION

The MAPK pathway is intricately connected with infection, immunity, and inflammation by way of cell signaling and activation of immune responses. MAPK is also involved in the pathophysiology of infections, including sepsis, a severe condition in which the immune system responds improperly to infection, leading to organ dysfunction and possible failure (10). MAPK pathways regulate immune cell functions such as macrophage activation, T-cell differentiation, and the production of pro-inflammatory mediators (11).

In sepsis, the dysregulated host response is characterized by organ dysfunction that can be serious and life-threatening. Sepsis is a condition that occurs when the body's immune response to infection causes widespread inflammation, leading

to tissue damage, organ failure, and potential death (12). Inflammation is a critical component of the immune response to infection but, if left unchecked, can cause severe tissue damage.

Both the MAPK and RIPK pathways contribute to the production of pro-inflammatory cytokines such as TNF, IL-1β, and IL-6 (5). These cytokines help fight infection but can lead to hyperinflammatory states if unregulated. During sepsis, activation of immune signaling pathways such as MAPK and RIPK becomes dysregulated. Hyperinflammation due to excessive cytokine production is often called a "cytokine storm". Along with cell death (both apoptotic and necroptotic), this cytokine storm is a key feature of sepsis (13), and therefore, controlling inflammation and balancing immune responses are critical to managing this disease.

Pathogens use integrins to enter cells (14). Integrins are transmembrane receptors that facilitate cell adhesion to the extracellular matrix, which transmits signals to the intracellular environment, a biological process known as "outside-in signaling" (15) (Fig.1). Integrins are involved in the activation and migration of immune cells that respond to pathogens. These proteins allow cells of the immune system to reach the site of infection by migrating through the walls of blood vessels (16).

By binding integrins or other cell surface receptors, pathogens can interact with host MAPKs and integrins to facilitate their own survival and induce MAPK activation (17,18). Integrins bind to the extracellular matrix or specific pathogens, triggering the activation of MAPKs such as ERK and JNK, which regulate inflammation and/or apoptosis (19). Bacteria can interact with integrins on epithelial cells, triggering MAPK pathways that lead to the production of inflammatory cytokines, which help induce an immune response (20). Some viruses are known to hijack the MAPK pathway to promote viral replication and avoid apoptosis; while bacterial pathogens can use integrins to enter cells and manipulate MAPK signaling to suppress immune responses or induce cell survival signals (21-23).

The onset of sepsis can cause a “cytokine storm” that is generated mainly by IL-1, TNF, and IL-6 (24). These cytokines are produced by various cells, including macrophages, and they can cause harm by damaging tissue and organs. Cytokines mediate inflammatory processes and activate the NF-kB, MAPK, and JNK signaling pathways (25).

Serine-threonine kinase 1 is an apoptosis signaling regulator and stress regulator that is expressed in nucleated cells and activates several kinases (26). The activation of kinase 1 induces transcription factors to generate inflammatory cytokines (27).

The body responds to infections through various signaling pathways, including the MAPK and RIPK pathways, which mediate immune and inflammatory responses (28). RIPKs are specifically involved in the decision of cells to choose their fate: whether to survive, to die, or to release inflammatory signals (29). Pathogens such as bacteria and viruses can trigger RIPK inflammation pathways, leading to activation of immune cells, the release of pro-inflammatory cytokines, and sometimes, exaggerated inflammation.

RIPK signaling plays a dual role in immune defense and inflammation (30). RIPKs are critical for regulating cell death and inflammatory signaling (31). RIPK1 and RIPK3, in particular, are involved in necrosis that occurs in response to infection and inflammatory stimuli (32). In infections, RIPK activation can help control the spread of pathogens by inducing cell death or exacerbating tissue damage which contributes to sepsis.

RIPK1 is promising therapeutic target for the cure of many neurodegenerative diseases. Phosphorylation of this kinase mediates apoptosis. RIPK1 regulates cell survival, apoptosis, and inflammation, while RIPK3 is more specifically involved in promoting necrosis. RIPK1 is the first member of the Ser/Thr RIPK family, and it is constitutively localized in the cytoplasm; however, nuclear translocation of RIPK1 has also been reported, although its function in the nucleus has not yet been determined (33,34). Indeed, RIPK1 has been implicated in TNF-induced cell death and has been proposed as a target for cancer therapy (35). RIPK1 regulates various enzymes, activates inflammatory responses, inhibits kinase activity, and reduces cell death by increasing resistance to TNF-induced necrosis (36).

CONCLUSIONS

Infections stimulate the immune system through MAPK and RIPK signaling, regulating inflammation and apoptosis. Pathogens often use integrins to enter host cells. Once inside, or after binding to the cell surface, pathogens activate MAPK pathways (ERK and JNK) to initiate immune responses and induce inflammation.

MAPK pathways are activated to defend the body, but pathogens often manipulate this pathway to support their replication, spread, and evasion of the immune system. These interconnected reactions make MAPK and integrins important players in the balance between immune defense and pathogen survival. Immune responses help fight infections, but their dysregulation (as occurs during sepsis), can lead to excessive inflammation and cell death, causing damage to tissues and cells. The study of these biochemical pathways is fundamental for the development of therapeutic strategies for sepsis and inflammatory diseases.

Conflict of interest
The authors declare that they have no conflict of interest.

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