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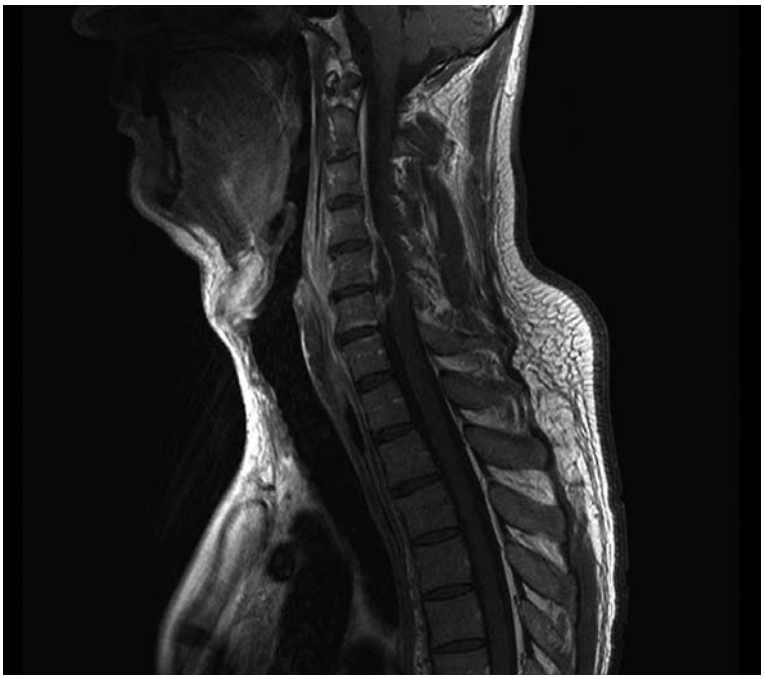

*A patient with neck pain and fever: what is your diagnosis?*



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VAN ZUIDEN COMMUNICATIONS

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# The Journal of Medicine

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EDITORIAL

# How academic is internal medicine in the Netherlands? A bibliometric analysis

**M. Levi**

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One of the most tangible 'production units' of science is research publications, and indeed the number of publications and the amount of citations these papers generate are often used as indicators of quantity and quality of research. Worldwide research efforts have increased over the last decades, resulting in an almost exponential increase in publications. Indeed, the number of PubMed entries reflecting medical-biological publications has rapidly increased over the last period; in 2008 PubMed indexed 769,009 articles, a figure that is almost double the number that was collected in 1998 (429,217). Despite often heard wailing and whining, clinical research has retained its position in the biomedical research output and has even grown substantially compared with fundamental research.[1] The position of the Netherlands in clinical research is traditionally strong and recent analyses show that this has not changed in the last few years.[2,3] In fact, in the field of Internal Medicine, the Netherlands occupies a third position in terms of impact and has a relatively high number of publications per 10,000 population (*table 1* and *figure 1*). Interestingly, several analyses have shown that this is not related to the financial input of the government in biomedical research. Instead, the amount of money from governmental sources is relatively small in the Netherlands compared with almost any other European country and the US.[4,5] In comparison with other countries in the world, the Netherlands also has a relatively high number of publications in the two leading clinical journals (the *New England Journal of Medicine* and the *Lancet*). A subdivision of the publications over various subdisciplines of Internal Medicine shows the strongest areas of Internal Medicine in the Netherlands as compared with Europe and the United States (*figure 2*). Interestingly, these figures coincide with the number of publications of each of these subdisciplines in the *Netherlands Journal of Medicine*.[6]

Bibliometrics may also provide some insight into the research productivity of Dutch physicians working in various subdisciplines of medicine. *Figure 3* provides an estimate of the average number of publications per staff member per five years in the eight academic departments of Internal Medicine in the Netherlands. It should be mentioned that this type of analysis may harbour some inaccuracies, as it is not always clear to which (sub)department a given staff member belongs

**Table 1.** *Top 10 countries worldwide in terms of average number of publications on Internal Medicine*

| Country | Impact | Citations | Average number of publications |
|---|---|---|---|
| Sweden | 21.17 | 81,722 | 3860 |
| United States | 20.83 | 2,015,339 | 96,733 |
| The Netherlands | 20.26 | 80,119 | 3954 |
| Denmark | 16.71 | 52,182 | 3123 |
| United Kingdom | 15.26 | 601,286 | 39,411 |
| Italy | 12.53 | 61,332 | 4893 |
| Canada | 12.45 | 155,665 | 12,507 |
| Australia | 10.33 | 91,193 | 8825 |
| Switzerland | 8.40 | 63,230 | 7527 |
| Japan | 7.35 | 32,475 | 3483 |

**Figure 1.** *Research output as reflected by publications per 10,000 inhabitants and number of publications in the New England Journal of Medicine or the Lancet per million inhabitants*

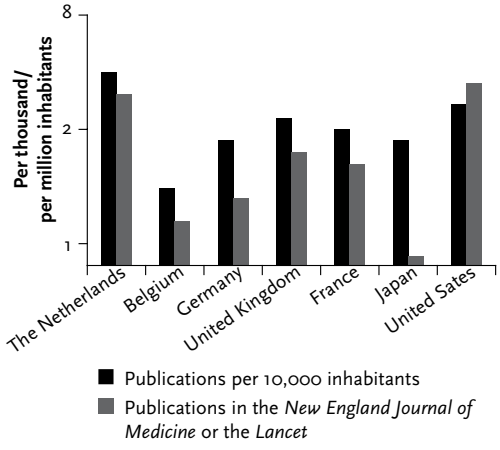


**Figure 2.** *Relative strength per subdiscipline of medicine*

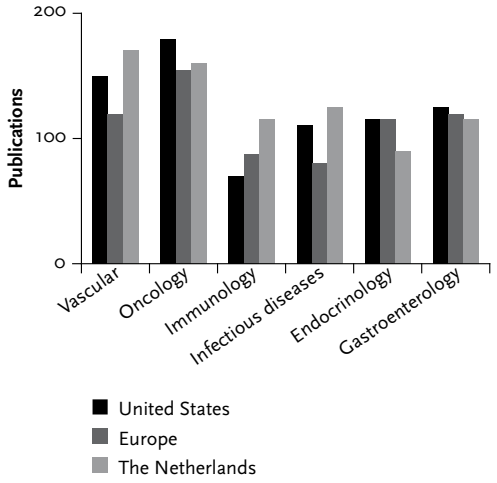



**Figure 4.** *Frequency of staff members in academic departments of Internal Medicine in the Netherlands related to their average yearly number of publications*

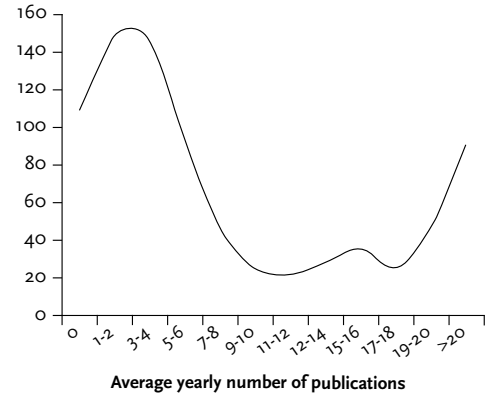



**Figure 3.** *Number of publications per staff member per five years in academic departments of internal medicine*

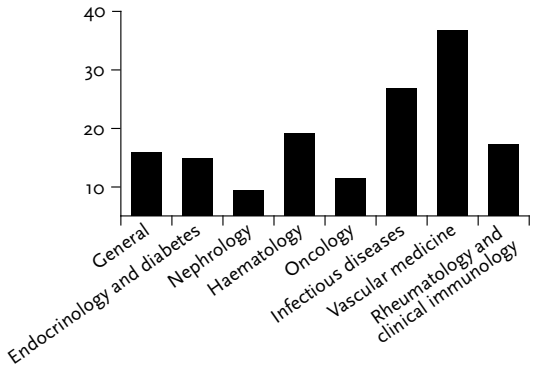
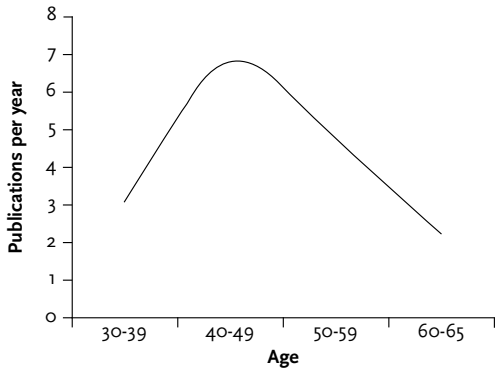



**Figure 5.** *Average yearly number of publications and the age of the academic internist in the Netherlands*




and only tenured staff has been included in the analysis. Even more interesting is the frequency of staff members with a given yearly average number of publications in the academic departments (*figure 4*). By far the most academic internists publish approximately two to seven papers each year, but apparently there is not a normal distribution. A group of about 110 academic internists do not publish at all, which may be due to the fact that these internists devote their time exclusively to patient care and teaching. In contrast, there is a substantial group of academic researchers in the departments of Internal Medicine that publishes more than 20 articles per year. Interestingly, the yearly number of publications varies with age, peaking between 40 and 55 years and, somewhat surprisingly, thereafter declining (*figure 5*). A potential explanation for this decline may be that senior staff members have to devote more time to management of their department and can thus spend less time on research.[7] It should be mentioned, however, that in the group with more than 20 publications per year the age group of older than 55 years is overrepresented.

Taken together, there is ample reason to be proud of the position of research in Internal Medicine in the Netherlands. Obviously, it is a challenge for the next decades to maintain this position and to become even more productive while keeping up the high quality.

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REVIEW

# Transfusion-related acute lung injury: a change of perspective

**A.P. Vlaar[1*], M.J. Schultz[1,2], N.P. Juffermans[1,2]**

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**Abstract: Two decades ago, transfusion-related acute lung injury (TRALI) was considered a rare complication of transfusion medicine. Nowadays, TRALI has emerged as the leading cause of transfusion-related mortality, presumably as a consequence of reaching international agreement on defining TRALI with subsequent increased recognition and reporting of TRALI cases. Specific patient populations such as critically ill patients have an increased risk of developing TRALI, which may be explained by the two-event hypothesis. The first event is the underlying condition of the patient resulting in priming of neutrophils. The second event is the transfusion of a blood product, after which either antibodies or bioactive lipids activate the primed neutrophils, resulting in pulmonary oedema. As opposed to the traditional view that TRALI has a good prognosis, TRALI may have a significant impact on morbidity and outcome, at least in specific patient groups. The association of transfusion with adverse outcome calls for blood product and donor management strategies aimed at decreasing the risk of acquiring TRALI. Excluding female donors from plasma donation seems to have reduced, but not prevented the occurrence of TRALI. Additional research is needed to determine whether the use of fresh blood products may be an additional measure to reduce TRALI. Studies are also needed to identify at-risk patients. In these studies, we advocate the use of the consensus definition to improve comparability of risk factors and outcome of TRALI across patient populations.**

KEYWORDS

Blood donor, critically ill, incidence, prevention, TRALI

## INTRODUCTION

Acute respiratory distress after transfusion of a plasma-rich blood product is known as transfusion-related (TR) acute lung injury (ALI). Of all adverse reactions associated with transfusion, TRALI is the most common and the most serious complication. According to the Food and Drug Administration and to several surveillance systems, TRALI has become the leading cause of transfusion-related death.[1-4] Originally, TRALI was thought to be an antibody-mediated reaction, in which antibodies in the blood product react with a matching antigen in the recipient, leading to pulmonary neutrophil activation and increased pulmonary capillary permeability and subsequent pulmonary oedema.[5] Although the exact incidence of TRALI is unknown, TRALI is considered to be a rare event. With supportive therapy, TRALI is generally reported to have a good prognosis.[6]

The above-described traditional outlook on TRALI has changed in recent years. The development of a case definition has greatly facilitated research and estimates of incidence of TRALI. Studies using this definition showed that TRALI occurs more frequently then previously reported, in particular in the critically ill and injured patient population.[7,8] Also, insight into TRALI pathogenesis has evolved. In addition to the original antibody hypothesis, a two-event hypothesis of TRALI has been postulated.[9,10] The first event is the patient's underlying clinical condition, including infection, surgery, or trauma, causing inflammation with priming of the pulmonary neutrophils. The second event is caused by the blood product. Either bioactive molecules which have accumulated during storage of cell-containing blood products or antibodies activate the primed neutrophils, resulting in permeability oedema. Previously regarded as a relatively self-limiting disease,[1,5,6,11] some observations suggest that TRALI may significantly contribute to morbidity and mortality in certain patient groups.[7]

In this manuscript, we describe the change in perspective on incidence, pathogenesis and outcome of TRALI. The impact of these changes on current and possibly implicated future management of TRALI is discussed.

## METHODS – SYSTEMATIC SEARCH OF THE LITERATURE

The Medline database was used to identify medical subject's headings (MeSH) to select search terms. In addition to MeSH terms, we also used free-text words. Search terms referred to aspects of the condition ("TRALI", "blood transfusion/adverse effects") as well as related topics ("storage", "human leukocyte antibodies", "red blood cells", "fresh frozen plasma" and "platelet transfusion"). All papers back to 1985 were assessed on relevance using the online abstracts. In addition, the reference lists of retrieved papers were screened for potentially important papers.

## TRALI DEFINITION

As distinguishing biomarkers are absent, TRALI is a clinical diagnosis. The lack of a consensus definition of TRALI has contributed to under-diagnosing of this syndrome. In recognition of this problem, a case definition of TRALI based on clinical and radiological parameters was formulated during a consensus conference and by the US National Heart, Lung and Blood Institute in 2004.[1,11,12] The definition is derived from the widely used definition of ALI and its more severe form acute respiratory distress syndrome (ARDS), as proposed by the North American-European Consensus Conference (NAECC) consensus.[13] These criteria include the acute onset of hypoxia with bilateral pulmonary infiltrates, no evidence of left ventricular overload and the presence of a risk factor for ALI/ARDS (*table 1*). TRALI is defined as the fulfilment of the definition of ALI within six hours after transfusion in the absence of another risk factor for ALI (*table 1*).[1,11,12]

Although this definition appears straightforward, a complicating factor is that the characteristics of TRALI are indistinguishable from ALI due to other aetiologies, such as pneumonia, sepsis or lung contusion. Using this definition would rule out the possibility of diagnosing TRALI in a patient with an underlying ALI risk factor who has also received a transfusion. To identify such cases, the term 'possible TRALI' was developed (*table 1*), which allows for the presence of another risk factor for ALI. Given the uncertainty of the relationship of ALI to the transfusion in possible TRALI, this term facilitates separate categorisation in surveillance systems to permit comparisons across systems.

**Table 1.** *Definition of transfusion-related acute lung injury (TRALI)*

**TRALI**

- Acute onset within 6 hours after a blood transfusion
- $PaO_2/FiO_2$ <300 mmHg
- Bilateral infiltrative changes on the chest X-ray
- No sign of hydrostatic pulmonary oedema (pulmonary arterial occlusion pressure <18 mmHg or central venous pressure <15 mmHg)
- No other risk factor for ALI present

**Possible TRALI**

All of the above but another risk factor for ALI present

## TRALI INCIDENCE

The incidence of TRALI has not been well established. Estimated incidence rates vary widely, ranging from 0.002% to 1.12% per product transfused and from 0.08 to 8% per patient transfused,[5,7,8,14-19] (*table 2*). The rates presented should be regarded with caution for several reasons. First, the definition used for TRALI differed between studies. Some required the presence of antibodies against human neutrophil antigen (anti-HNA) or against human leukocyte antigen (anti-HLA),[4,5] whereas others used only clinical criteria.[7,17,18] In addition, surveillance systems in some countries, including the United States and the Netherlands, use an alternative definition to the consensus definition, in which imputability is scored.[19,20] A case definition which rules out the possibility of TRALI when another ALI risk factor is present will lead to lower incidence rates compared with studies that have allowed for an alternative risk, i.e. possible TRALI. In critically ill patients, alternative ALI risk factors are often present. A prospective study in this patient group reported a high incidence of suspected and possible TRALI cases taken together.[7] However, the high incidence is probably not merely a consequence of applying a broader definition. In addition to fulfilling the clinical diagnosis, immunological workup of these cases showed the presence of HLA/HNA antibodies in the plasma of associated donors, contributing to the suspicion that most of these were indeed TRALI cases. Second, the method of surveillance differs between studies. Obviously, studies with an active case investigational approach yield higher incidence rates than outcomes of passive surveillance systems. Third, the population under investigation differs between studies, which may hamper comparability of the available incidence data. Finally, in the absence of a biomarker, TRALI is diagnosed using clinical and radiological parameters. Subjective interpretation of clinical findings may contribute to differences in estimates of incidence.

Studies that have applied the consensus definition formulated in 2004 report higher TRALI rates then before, in particular in critically ill patients.[7,8] These findings support the general notion that TRALI is

**Table 2.** *Overview of incidence reports of TRALI*

| Reference | Type of study and inclusion | Population | Country | Study year | Incidence of TRALI | |
|---|---|---|---|---|---|---|
| | | | | | Per patient transfused | Per product transfused |
| Popovsky[5] | Retrospective Active | Hospital | United States | 1983 | N/A | 0.02%* |
| Henderson[15] | Retrospective Passive | Regional | Australia | 1981-89 | N/A | 0.001% |
| Clarke[14] | Retrospective Passive | Hospital | United States | 1994 | N/A | 0.33%** |
| Silliman[16] | Retrospective Active | Hospital | Canada | 1991-95 | 0.08% | 0.22%** |
| Wallis[18] | Retrospective Passive | Hospital | United Kingdom | 1991-2003 | N/A | 0.01%* |
| Wiersum[19] | Retrospective Passive | National | The Netherlands | 2002-05 | N/A | 0.002% |
| Rana[8] | Retrospective Active | ICU | United States | 2003 | 1.8% | 0.26% |
| Vlaar[55] | Retrospective Active | ICU | The Netherlands | 2004-07 | 5.1% | 0.9% |
| Gajic[7] | Prospective Acive | ICU | United States | 2005-07 | 8% | 1.12% |

***Incidence determined only in plasma products transfused; **incidence determined only in platelets concentrate products transfused.**

under-diagnosed and under-reported.[3,11] An increase in reporting may have occurred with increased awareness of TRALI. Nevertheless, a look-back study, in which recipients of blood products from a donor linked to a TRALI fatality were analysed for symptoms of TRALI, showed that TRALI was frequently not recognised.[21] Therefore, under-diagnosing is not merely a consequence of awareness, but also of a failure to recognise the syndrome.

A rise in incidence has also been reported by national surveillance systems,[1,2,19,20] suggesting that the rise in incidence is not limited to the critically ill patient population. Rather, before the consensus definition, the presence of other risk factors for ALI excluded critically ill or injured patients from a diagnosis of TRALI and consequently, from estimates of the incidence of TRALI in this patient population. The consensus definition has made estimates of incidence in this patient group possible. Overall, the consensus definition may also have facilitated clinical recognition of TRALI cases.

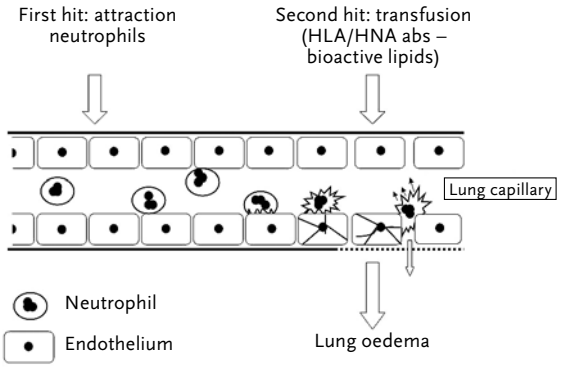
The more recent figures suggest that TRALI may be a significant health problem. Several other observations support this notion. Transfusion of blood products is associated with development of respiratory complications in ICU patients, including ALI.[22-24] Also, a liberal transfusion strategy was associated with an increased risk of ALI when compared with a restrictive policy.[25] Although the temporal relation in most of these studies was not defined, it is likely that a significant number of these patients may have had TRALI. Therefore, the traditionally held view that TRALI is a rare event may not hold true, at least not in the intensive care unit.

The observations that blood transfusion is associated with respiratory complications are in keeping with the two-event hypothesis of TRALI, discussed below, in which transfusion worsens microvascular injury characteristic of ALI.

## TRALI PATHOGENESIS

Any cell-containing blood product or plasma-rich blood product can cause TRALI. The pathogenesis has not been fully elucidated. Two hypotheses have been formulated. The first hypothesis suggests that TRALI is caused by donor antibodies against human neutrophil antigens (HNA) or human leukocyte antigens (HLA) in the lungs of the recipient.[5,26] However, the association between HLA antibodies in donor plasma and TRALI is not very strong. A significant fraction of TRALI cases have no detectable antibodies.[21,27,28] Also, many antibody-containing blood products fail to produce TRALI.[29-31] An alternative hypothesis implicates a two-event model.[9,32,33] The first event is an inflammatory condition of the patient (e.g. sepsis, recent surgery) causing sequestration and priming of neutrophils in the pulmonary compartment (*figure 1*). The second event is the transfusion, containing either antibodies or bioactive lipids that have accumulated during blood storage, stimulating the primed neutrophils to release proteases. The result in both hypotheses is endothelial damage, capillary leak and extravasation of neutrophils.[33-35] The two-event model is supported by experimental studies, in which bioactive lipids as well as outdated blood products

**Figure 1.** *Pathophysiology of transfusion-related acute lung injury (TRALI)*




**Neutrophils are attracted to the lung by release of cytokines and chemokines. Firm adhesion to the endothelium of the lung capillaries is realised. Neutrophils are then activated by the 'second hit' of bioactive lipids or HLA/HNA antibodies. This results in alveolar capillary damage and leakage of fluid into the alveolar space, resulting in the clinical picture of TRALI.**

have been used to cause TRALI after a priming hit.[32,33,36] Also, observational studies report associations between prolonged storage of blood products and ARDS in the critically ill.

However, the premise that only patients in a poor clinical condition develop TRALI does not hold true in some case reports, in which a relatively active patient and a healthy research volunteer developed TRALI.[11,37] A threshold model has been suggested,[9] in which a threshold must be overcome to induce a TRALI reaction. Factors that determine the threshold are the predisposition of the patient that determines priming of the lung neutrophils and the ability of the mediators in the transfusion to cause activation of primed neutrophils. A strong antibody-mediated response can cause severe TRALI in an otherwise 'healthy' recipient. When activation status is too low, it is possible that priming factors in the transfusion are not strong enough to overcome the threshold. This would explain why TRALI does not develop in a transfused patient even when an antibody-antigen match is present. In a critically ill patient with predisposing factors for ALI, such as pneumonia, sepsis or trauma, transfusion of mediators with low neutrophil-priming activity may be sufficient to overcome the threshold to induce a TRALI reaction.

The above-mentioned model underlines the concept that critically ill patients are susceptible to a TRALI reaction due to an inflammatory response, resulting in priming of pulmonary neutrophils.[1,11] If indeed risk factors for ALI of any origin predispose to TRALI, the multiple possible 'first events' may explain the increased incidence of TRALI in the critically ill, when compared with the general hospital population.

## TRALI SYMPTOMS

In its fulminant presentation, TRALI is indistinguishable from ALI secondary to other causes. Symptoms include rapid onset of respiratory distress due to severe bilateral pulmonary oedema. Chest radiographs classically demonstrate bilateral 'white out' lungs, indistinguishable from hydrostatic pulmonary oedema,[38] but in the first few hours, a patchy pattern may be observed.[5] Typically, patients develop the symptoms of TRALI within one to two hours after transfusion, but an onset of six hours has also been accepted. Some case reports indicate an incubation period of up to 48 hours.[39,40] Hypotension is not a consistent finding. Transient neutropenia has been described.[41]

Most clinical cases described in the medical literature refer to the above-mentioned severe presentation.[42-45] However, there is growing appreciation that milder forms of respiratory distress may still represent the syndrome. A spectrum of severity is noted in TRALI cases, ranging from transient dyspnoea to fulminant ALI/ARDS.[1,6] Reports from a donor with neutrophil antibodies involved in multiple transfusion reactions showed a wide variety of transfusion reactions, including mild symptoms that do not meet the definition of TRALI.[46]

A particular challenge is the distinction between TRALI and transfusion-associated circulatory overload (TACO), as clinical and radiological features are similar.[47] The TRALI definition holds that the pulmonary artery occlusion pressure should not exceed 18 mmHg (*table 1*), whereas in TACO, elevated wedge pressure is a common finding. However, the scenario that TRALI and TACO are mutually exclusive is probably not true. Indeed, a considerable number of patients with clinical criteria for ALI are misclassified after measurement of the pulmonary artery occlusion pressure.[48] Vice versa, pulmonary oedema due to capillary leak, as found in TRALI, may also increase pulmonary arterial pressure, thereby no longer satisfying the TRALI consensus definition. Other markers, such as brain natriuretic peptide and N-terminal pro-brain natriuretic peptide, were not helpful in discriminating between TACO (or cardiogenic pulmonary oedema) and TRALI,[49] rendering distinction between TRALI and TACO a continuing challenge.

Considering the spectrum of disease severity, including a mild presentation, as well as the difficulty in distinguishing TRALI from circulatory overload, TRALI may often be overlooked. Failure to recognise TRALI clinically may contribute to low incidence rates which may represent only a small part of lung injury inflicted by transfusion. Efforts to increase recognition of the TRALI syndrome are important to determine when to start complex and expensive immunological workup of involved donors in a suspected TRALI case and subsequent donor exclusion to prevent future TRALI reactions.

## TRALI OUTCOME

It is often stated that TRALI differs from ALI due to other causes in terms of outcome. Whereas mortality of ALI is 40 to 60%,[50] the majority of TRALI patients improve within 48 to 96 hours after the insult, when appropriate respiratory support is supplied. The mortality rate of TRALI is considered to be low, around 5 to 10%.[5,6,11,16] Also, in contrast to many ALI patients who develop irreversible lung injury, it is stated that pulmonary function of TRALI patients usually recovers, without apparent structural damage such as the occurrence of fibrosis.[6] However, data on outcome of TRALI are sparse, mostly based on case series.

In contrast with the above, studies in critically ill or injured patients report that blood transfusion is associated with considerable morbidity and mortality. Transfusion of blood is an independent risk factor for developing ALI in trauma patients and in ICU patients,[22-24,51] thereby increasing length of ICU and hospital stay. Adverse outcome appears to be associated with the number of units transfused and with transfusion of fresh frozen plasma or platelets.[24,52] An association of transfusion with mortality was found in established ALI patients,[23] and in patients after cardiothoracic surgery.[53] The impact of red blood cell transfusion on outcome was reviewed recently, showing that red blood cell transfusion increased the risk of developing ALI and contributed to mortality in ICU, trauma and surgical patients.[54]

Of note, these studies show an association between transfusion and adverse outcome, not between TRALI and outcome. The association between TRALI and outcome has still not firmly been established. However, although the time frame was generally not determined in these studies, it is likely that some of these patients complied with the TRALI definition. Indeed, mortality of TRALI was found to be higher compared with transfused controls in a critically ill patient population.[7] In addition, we have recently performed a retrospective study of TRALI in a large cohort of over 5000 critically ill patients admitted to our ICU, using the consensus definition. We found that patients developing TRALI had a prolonged ICU stay and were mechanically ventilated for longer compared with transfused controls.[55] Mortality was higher in the TRALI group compared with the transfused controls (24 *vs* 13%, p=0.04).

Importantly, from these reports on the association between transfusion and adverse outcome, it is not clear to what extent the transfusion or other ALI risk factors contributed to mortality. These observations have the potential limitation that blood is more frequently administered to sick patients and sick patients more frequently develop complications and die. Therefore, whether transfusion is a marker or a mediator of disease is an important question that remains to be answered.

## TRALI MANAGEMENT

Management of TRALI is supportive, as is the management of any patient with permeability oedema. All patients require additional oxygen and mechanical ventilation is unavoidable in 70 to 90%.[5,18] In line with treatment of ALI patients, it could be speculated that a restrictive tidal volume ventilation should be applied to avoid worsening of lung injury.[56] Specific treatment strategies for TRALI, however, do not exist.

TRALI management consists mainly of preventing future adverse reactions. A patient in whom TRALI is suspected should be reported to the National Blood Bank for a serological workup of the recipient and the implicated donors on the presence of HLA and HNA antibodies. Incompatibility is tested by cross-matching donor plasma against recipient's leucocytes. A donor with antibodies which are incompatible with the patient is excluded from further donation of blood for transfusion products. As stated before, the two-event hypothesis does not exclude the role of antibodies in the occurrence of TRALI. Therefore, we would like to underscore that 'possible TRALI', i.e. a TRALI reaction in a patient with an additional TRALI risk factor, should be reported to the National Blood Bank, to allow for reliable incidence estimates in this patient group and to determine whether serological workup should be initiated to identify an implicated donor.

The two TRALI theories yield different approaches to further preventive strategies. In the antibody-based theory, blood products with the highest antibody content (fresh frozen plasma and platelet concentrates) would be more likely to cause TRALI. Most donors associated with cases of TRALI are multiparous women. The likelihood of HLA allo-immunisation increases with the number of pregnancies, from 8% in the absence of previous pregnancies up to 26% of multiparous women harbouring HLA antibodies.[57] The clinical significance of donor gender was demonstrated in two studies in critically ill patients reporting worsened oxygenation after fresh frozen plasma (FFP) transfusion from (multiparous) female donors.[8,58] Given the association of female donors with TRALI, the UK National Blood Service has deferred women from plasma donation since 2003. Since then, reports of TRALI cases have diminished. It should be noted, however, that the UK haemovigilance system only reports a TRALI case in the presence of antibodies. Two clinical studies have appeared, showing that excluding female donor plasma may prove effective. In the UK, the onset of ALI in patients receiving multiple transfusions while undergoing repair of a ruptured abdominal aortic aneurysm was reduced from 36 to 21%.[59] Excluding all females from plasma donation was copied by the Dutch National Blood Service in 2006. We showed that this policy also reduced, but did not prevent, the occurrence of

ALI in a mixed medical-surgical population of critically ill patients.[17]

Regardless of which theory one accepts, the deferral of women from plasma donation will not prevent all cases of TRALI. Measures aimed at preventing two-event TRALI include an alternative approach. Obviously, less transfusion results in less TRALI. In the critically ill, a restrictive transfusion trigger is well tolerated and associated with improved outcome in selected patient groups.[25] However, restrictive guidelines for erythrocyte transfusions are not always followed.[60] Also, blood transfusions are not avoidable. An alternative approach which is increasingly receiving attention is the transfusion of fresh red blood cells. Stored red blood cells undergo functional and morphological changes over time, referred to as storage lesions. Studies on the impact of aged blood on respiratory complications have yielded conflicting results. In cardiothoracic surgery patients, respiratory insufficiency and mortality was lower in patients who had received blood stored for less then 14 days compared with patients that had received blood stored for more then 14 days (7.4 *vs* 11.0%, p<0.001).[61] However, similar studies did not confirm these findings.[62,63] The age of platelets has also been associated with ALI in a clinical observational study.[16] Well-designed prospective studies are needed to determine whether patients 'at risk' for TRALI (i.e. critically ill or injured patients) would benefit from a differential transfusion policy using fresh products only.

Without doubt, both the deferral of female donors and the use of fresh blood only, has serious consequences on blood availability. For the sake of the patient, product management strategies as well as donor-exclusion policies should be aimed at decreasing the risk of acquiring TRALI without impeding a continuous reliable blood supply.

## CONCLUSION

The perspective on TRALI has changed in the past years. TRALI is an under-estimated health problem, with a significant impact on outcome in specific patient groups. Recognition of the association of transfusion with pulmonary injury is important, in terms of adherence to restrictive transfusion policies, but also in terms of reporting suspected TRALI cases for immunological workup to prevent future reactions. We propose to use the consensus definition rather then national protocols to identify TRALI cases to improve comparability of incidence rates, course of disease and outcome in different patient populations. Excluding females from plasma donation has reduced, but not prevented TRALI. Future research is needed to determine whether transfusion of fresh blood will only reduce the risk of a TRALI reaction in at risk patients.

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REVIEW

# Immune reconstitution inflammatory syndrome: immunopathogenesis, risk factors, diagnosis, treatment and prevention

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## ABSTRACT

**Immune reconstitution inflammatory syndrome (IRIS) occurs in a subpopulation of HIV-infected patients after the introduction of antiretroviral therapy (ART). The purpose of this review is to describe the immunopathogenesis, risk factors, diagnostic problems, treatment and prevention of IRIS. A literature search was performed and finally 15 recent articles were selected.**

**The immunopathogenesis of IRIS is characterised by a dysbalanced restoration of the immune system resulting in pathological inflammation. Risk factors are low baseline CD4-cell count, an excellent virological response, an increased antigenic burden of an opportunistic infection and early initiation of ART after an opportunistic infection. The differential diagnosis of IRIS is elaborate. Treatment options include discontinuation of ART, corticosteroids or pathogen-specific therapy.**

**Diagnosis can be difficult, because IRIS may manifest with a diverse range of clinical presentations. Adopting one case definition and performing more research regarding diagnosis and treatment of IRIS are important recommendations for future studies.**

## KEYWORDS

Antiretroviral treatment, HIV infection, immune reconstitution inflammatory syndrome

## INTRODUCTION

Immune reconstitution inflammatory syndrome (IRIS) is seen in a subpopulation of HIV-infected patients after the initiation of antiretroviral therapy (ART). Most HIV-infected patients improve after the introduction of ART because ART will reduce the HIV-RNA and boost up the immune system. In some patients another response is seen after starting ART. Their clinical condition worsens and they develop symptoms compatible with infectious diseases such as tuberculosis, herpes zoster, cryptococcosis, toxoplasmosis or bacterial pneumonia. This phenomenon has been termed IRIS and has been thought to be due to the restored ability to mount an inflammatory response after the initiation of ART.[1]

There are two common clinical scenarios: unmasking IRIS and paradoxical IRIS. In unmasking IRIS, the infection is newly identified after the initiation of ART, and usually the provoking pathogen is viable. In paradoxical IRIS, the infection was previously treated but worsened clinically after ART initiation and the causative pathogens can be either viable or non-viable.[1]

Studies have demonstrated that 10 to 32% of patients starting ART will develop IRIS.[2] Hospital admission is not uncommon, medical regimens have to be revised and this brings discomfort to the patient. For example, in a prospective cohort study among HIV-infected patients starting ART in Ethiopia, 76% of hospital admissions after ART introduction were because of IRIS.[3] The biggest problems are faced in the developing countries, where ART is now used on a much larger scale. Due to the high incidence of tuberculosis (TB) and the limitations in diagnostic procedures, diagnosis and treatment of IRIS can be more troublesome in these poor resource settings.[1]

In this review, we provide an overview on the pathogenesis, risk factors, diagnostic problems, treatment, and prevention of IRIS.

## LITERATURE SEARCH

To address this topic, a search was performed in the PubMed database with the following terms: immune recovery syndrome OR immune reconstitution inflammatory syndrome OR immune restoration disease (#1) and (HIV) OR (AIDS) (#2). The last-mentioned terms were added because IRIS is also seen in some autoimmune diseases and malignancies, and we wanted to limit our study to HIV/AIDS. Limitations were: published in the last ten years, humans, English, clinical trials, meta-analyses, practical guidelines, randomised controlled trials and reviews. Studies that focused too much on one particular case or type of IRIS were excluded, because the purpose of this article was to describe IRIS in its general form.
Search #1 resulted in 1753 citations and search #2 resulted in 276,626 citations. The two searches were combined with the term "AND", this yielded 950 citations (#3). After adding the limits mentioned above, a total of 192 articles remained. The titles and abstracts of these articles were reviewed and judged on relevance. Finally, 13 articles were judged as being relevant. Three more articles were retrieved by using references, 'linked articles' or suggested by one of the reviewers. Further details on the articles are addressed in *table 1*.

## IMMUNOPATHOGENESIS

When we look at IRIS, one of the most striking features is that the clinical presentation depends heavily on the type of underlying infection.[1] This suggests that an antigen-driven process is going on in which a specific immune response is generated. Furthermore, we see an inflammatory response that is exaggerated. This could be explained by the fact that mechanisms that normally limit inflammation are missing.[4]
Two types of T cells are important in this matter, the pro-inflammatory TH17 cell and the regulatory T cell (Treg). The Treg suppresses proliferation of effector cells of the immune system and their cytokine production.[4] In a normal situation, the ratio between TH17 cells and Tregs is 2:1.[5] During immune reconstitution this ratio may be disturbed. Seddiki *et al.* hypothesised that Tregs could be defective in either numbers and/or function and therefore unable to ensure the physiological equilibrium of the immune system in patients with IRIS. They examined Treg frequency and, in contrary to what they expected, found a significant expansion of Tregs in IRIS patients compared with controls. The ratio of Treg to effector cells was also increased. However, when they performed *in vitro* suppression assays with these Tregs, they detected abnormalities in their function in IRIS patients.[5] Tregs of IRIS patients are less effective in regulating homeostasis of the immune system, because they show blunted ability to suppress the release of pro-inflammatory cytokines.
IL-7 is a haematopoietic growth factor and induces differentiation of the effector cells of the immune system and IL-7 levels inversely correlate with the CD4+ T-cell count.[4] HIV-infected patients with a low CD4 cell count before starting ART normally have high levels of IL-7. Seddiki *et al.* found that despite marked CD4 reconstitution in IRIS patients following ART, high IL-7 levels persisted, in contrast to treated HIV-infected patients without IRIS, in whom plasma IL-7 levels decreased progressively after ART when their CD4 cell count increased. So in theory, IL-7 levels could be used as a diagnostic measure for IRIS in the future.
Examination of the histopathological characteristics and inflammatory cell infiltrate of affected tissues or organs has demonstrated that CD8 T cells predominate in IRIS that is provoked by viruses, such as JC virus and cytomegalovirus. In contrast, granulomatous inflammation usually predominates in IRIS that is provoked by fungi such as *Histoplasma* species and cryptococci, by protozoans such as *Leishmania* species, mycobacteria such as *M. tuberculosis, Mycobacterium leprae,* and by nontuberculous mycobacteria. This would support the idea that the immunopathogenesis of IRIS is dependent on the provoking pathogen.[1]

**Table 1.** *Overview of the included case-control studies*

| Author (reference) | Study type | Number of included patients | Number of included controls | Follow-up period | Subject covered |
|---|---|---|---|---|---|
| Klotz[3] | Prospective | 74 | 15 | 6 months | Incidence, clinical presentation, management in a resource-poor setting |
| Seddiki[4] | Cross-sectional | 8 | 6 | N/A | Immunopathogenesis |
| De Boer[5] | Retrospective | 17 | 20 | 12 months | Risk factors, clinical and immunological characteristics |
| Meintjes[6] | Prospective | 80 | 20 | Not reported | Diagnosis, management in a resource-poor setting |
| Stone[7] | Retrospective | 37 | 15 | Not reported | Immunopathogenesis |
| Manabe[8] | Prospective | 49 | 196 | 6 months | Risk factors, treatment |
| Meintjes[9] | Prospective | 129 | 0 | 2 months | Immunopathogenesis |

## RISK FACTORS

Four factors show association with an increased risk for developing IRIS.

The first one is a low baseline CD4 T-cell count. When CD4 T cells are <200 cells/μl before ART initiation, patients are more likely to develop IRIS.[4] This is due to the greater risk of an opportunistic infection, more progressive damage to the immune system and disruption of regulatory mechanisms. This risk factor has particular implications for populations in developing countries, where persons are more likely to have advanced AIDS, co-infection with opportunistic infections, and lower CD4 T-cell counts when they initiate treatment. Furthermore, in a case-control study from the Netherlands it was demonstrated that the IRIS cases had a significantly higher-fold increase in CD4 T cells compared with controls.[5]

A second risk factor is an excellent virological response. Patients with a >2 log drop in HIV-1 RNA after 90 days of ART are at higher risk for IRIS. For example, it has been shown that in ART pretreated populations, where HIV virological resistance is more common, only those patients who respond to ART are at risk for IRIS.[10]

The third risk factor is an increased antigenic burden of an opportunistic infection at the initiation of ART. In a retrospective cohort study of TB patients, those with disseminated TB or extra-pulmonary TB had a greater incidence of IRIS compared with those with a lower antigenic burden with only a pulmonary infection.[10]

Therefore, the fourth risk factor is early initiation of ART after an opportunistic infection. Persons starting ART within two months after an opportunistic infection appear to have anywhere from zero to up to ten-fold risk of IRIS.[10] It still remains unclear what the optimal timing is for starting ART in patients with recent opportunistic infections. With an early start, the risk of IRIS is greater, and with a delayed start, the risk of death and new AIDS events increases. A recent study contradicts the findings of Bonham *et al*. In this study 282 patients with opportunistic infections (excluding TB) were enrolled, and randomised to early ART initiation *vs* delayed ART initiation. They concluded that early ART does not lead to an increase in IRIS in non-TB opportunistic infections.[11] This evidence makes early initiation of ART after an opportunistic infection questionable as a risk factor for IRIS.

Current research has demonstrated that different types of IRIS are associated with different genetic profiles. Patients with cytomegalovirus-related IRIS have been found to have increased frequency of human leukocyte antigen (HLA) B44 haplotypes compared with patients who do not develop IRIS. Specific cytokine gene polymorphisms that play a key role in decreasing cytokine production have been reported to be protective against mycobacterial- and herpes virus-associated IRIS.[10]

## DIAGNOSIS

Unfortunately, there is no diagnostic test for IRIS and the differential diagnosis is complex, including treatment failure of ART, failure of treatment of an opportunistic infection, drug interactions, drug toxicity or an alternative opportunistic infection. The diagnostic problems of tuberculosis-related IRIS (TB-IRIS) have been studied the most and will give us a good insight into the problem.

In countries with high rates of TB, an emerging complication of ART is TB-IRIS. TB-IRIS manifests with new, worsening or recurrent symptoms, signs or radiological manifestations of TB after ART is initiated (*table 2*). This pattern is seen in 8 to 43% of patients who start ART while receiving TB treatment.[6]

Concurrent with the increase in prevalence of TB-IRIS, there is also an emergence of multidrug-resistant (MDR) and extensively drug-resistant TB, especially in Southern Africa where HIV infection is highly prevalent. Treatment of TB-IRIS is usually with corticosteroids and it is therefore very important to determine the cause of deterioration in patients with TB during ART. Adjunctive corticosteroid therapy may worsen an already immunosuppressed patient's condition if it is used in the presence of incompletely effective TB treatment or another opportunistic infection.

In a prospective cohort study from Cape Town, South Africa, 100 patients who were considered to be likely cases of TB-IRIS were evaluated. In this area, routine TB drug susceptibility testing is not performed for new

**Table 2.** *Case definitions for tuberculosis (TB) immune reconstitution inflammatory syndrome (IRIS)*[8]

**Criteria that must be met for the diagnosis of TB IRIS before the initiation of cART**

- Microbiological, histological, or very strong clinical evidence of TB
- Initial improvement of >1 of the following during multidrug TB treatment: symptoms, Karnofsky score, weight, fever, clinical signs, or radiographic findings
- The infecting strain of *Mycobacterium tuberculosis* is susceptible to rifampin (if this result is available)
- The patient was receiving antitubercular therapy when cART was initiated

**Criteria that must be met for the diagnosis of TB IRIS within three months after the initiation of cART**

- New or recurrent TB-related symptoms and/or
- New or worsening TB manifestations, such as >1 of the following: new or expanding lymph nodes, new or expanding tuberculous cold abscesses, new or expanding intracranial tuberculomas, new or expanding pulmonary infiltrates (radio graphically confirmed), new or recurrent tuberculous meningitis (after exclusion of bacteria and fungi), new or enlarging serous effusions (pericardial, pleural, or ascitic; radiographically confirmed), new or worsening granulomatous hepatitis, new or worsening granulomatous infiltration of bone marrow, other new or worsening tuberculous lesions

**No other opportunistic disease to explain the new or recurrent symptoms and/or new or worsening**

TB cases. The clinical case definitions that were used for TB-IRIS are listed in *table 2*. Undiagnosed drug-resistant TB was present in 10.1% of patients who presented with TB-IRIS, once those with alternative diagnoses and TB with known drug-resistance were excluded.[6] Therefore, corticosteroids should be used with caution for patients with presumed TB-IRIS until results of drug-susceptibility testing are known.

When we look from a more general perspective, it is important to note that IRIS is a *diagnosis per exclusionem* which means that first all other possible causes of clinical worsening should be ruled out before we can conclude that the patient has IRIS.

## TREATMENT AND PREVENTION

Prevention and treatment of IRIS is difficult because no prospective controlled clinical trials concerning this topic have yet been published. There is one ongoing study (www.controlled-trials.com/mrct/search.html, accessed on 1 June 2009). When it comes to prevention, initiation of ART before advanced immunosuppression would be expected to reduce the risk of IRIS because advanced immunosuppression increases the risk for opportunistic infections, which is in itself a risk factor for IRIS.[10] To prevent unmasking IRIS, a thorough screening for active opportunistic infections before ART initiation is critical, because patients with advanced immunosuppression may have atypical or minimal symptoms owing to the absence of an inflammatory response. The screening for TB is difficult because the sensitivity of chest radiography and sputum smear examination in diagnosing active TB is reduced in HIV-infected persons.[12]

Early initiation of ART after an opportunistic infection has been identified as a risk factor,[10] but recent evidence contradicts these findings, at least for cases of non-TB-IRIS. In the case of TB-IRIS, the World Health Organisation (WHO) recommends ART initiation two weeks to two months after TB treatment is started in patients with a CD4 <200 cells/µl, but delaying in patients with higher counts. For other opportunistic infections no official recommendations have been established, so the clinician has to weigh the risks that come with delaying ART and advanced immunosuppression against the risks of IRIS.

Treatment of IRIS should be started after all other alternatives are ruled out and can be categorised in four different approaches, which can be used as mono or combination therapy.[13,14] The four approaches are: temporary ART discontinuation until the clinical condition has improved, use of non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids, pathogen-specific therapy or other therapy.

ART interruption should be recommended only for patients with severe, life-threatening symptoms until their condition is stabilised. IRIS can recur during re-initiation of ART, so this has to be monitored carefully. However, stopping ART in the setting of incompletely suppressed HIV replication may be associated with an increased risk of antiretroviral resistance.[15]

The use of drugs which can modulate the immune response, such as NSAIDs or corticosteroids, has been proposed. NSAIDs are advised for the management of mild and moderate cases, and corticosteroids for the individuals with severe or life-threatening disorders.[13] On the other hand, corticosteroids have been shown to be associated with an excess of Kaposi's sarcoma and herpes virus reactivation in HIV-infected patients with low CD4 counts but not in patients with increasing CD4 counts after initiation of ART.[12] The exact doses and duration of corticosteroid treatment have not yet been established. In a report of 49 cases of IRIS related to various infections, the median duration of prednisone treatment was 138 days.[8]

Pathogen-specific therapy should be started or continued in the case of unmasking or paradoxical IRIS. Other therapy includes needle aspiration of cold abscesses in TB-IRIS, therapeutic lumbar punctures and other drainage procedures for cryptococcal meningitis-IRIS and surgery for complications such as bowel perforation.[12]

## DISCUSSION

IRIS can be seen as a condition in which the immune system improves after introduction of ART, but is exaggerated, due to lack of homeostatic regulation. Clinically, the syndrome is very diverse, but a distinction can be made between paradoxical and unmasked IRIS. The most important risk factors for IRIS are a low baseline CD4 T-cell count, an excellent virological response, an increased antigenic burden of an opportunistic infection and early initiation of ART after an opportunistic infection. Diagnosis of IRIS is difficult because it has to be differentiated from treatment failure, drug interactions, non-compliance or an alternative opportunistic infection. Treatment options include discontinuation of ART, corticosteroids or pathogen-specific therapy.

This review has some limitations. Because studies on specific cases or forms of IRIS were excluded, the results of our search give an impression of the phenomenon of IRIS as a whole, in a more general perspective. Since the clinical presentation of IRIS is so diverse and depends on the underlying condition, the results presented here may not be applicable to each individual case. Furthermore, the cohorts of IRIS patients included were small, ranging from eight[4] to 129 patients.[9] The clinical heterogeneity of the syndrome cautions against drawing conclusions from

limited numbers of patients. Secondly, the follow-up period ranged from two months[9] to six months.[8] IRIS usually occurs within three months of ART introduction, but may also occur when a failing ART regiment is switched to a virally suppressive one or when ART is resumed after a temporarily interruption.[16] It is possible that cases of IRIS were missed because of the short follow-up period, or that only the most severe cases were seen because they tend to occur early after ART initiation. Despite the limitations of these studies, we think that IRIS is a very prevalent phenomenon especially in resource-poor countries and that research for diagnostic tests (as for example IL-7) and best treatment strategies (agent choice and duration) are urgently warranted.

Seddiki's study[4] needs to be mentioned separately. In this study the central role of the regulatory T cell was demonstrated for the first time. Their data have been adopted by many other researchers in the field. But it should be noted that Sedikki used only eight IRIS patients and six controls, who were all in late stage HIV (CD4 <50 cells/µl). This makes it difficult to generalise their results to a bigger population of IRIS patients.

There is a big difference in HIV prevalence and treatment between resource-poor countries and the Western world. In the resource-poor countries, the triple coincidence of very high TB rates, an expanding HIV epidemic and the large-scale roll-out of ART has led to a large increase in the number of cases of IRIS, especially TB-IRIS.[11] HIV-infected patients in these areas usually start ART with lower CD4 cell counts and a higher burden of opportunistic infections, which makes them more susceptible to IRIS. Diagnostic tests for opportunistic infections are not always available.[2]

One of the biggest problems faced in the IRIS-research field is the fact that there is not one case definition of IRIS that is used by all researchers. The International Network for the Study of HIV-associated IRIS (INSHI), has set up a list of criteria for the diagnosis of IRIS.[15] Unfortunately, these criteria are not incorporated by the researchers in their case definitions. Rather, they use the case definitions that are proposed in the latest review. If different criteria for IRIS are used in different studies, it is not possible to combine the results and increase the evidence that is available on the subject.

Lastly, the evidence for the benefits of corticosteroids in the treatment of IRIS is very poor. At present, there is no evidence from clinical trials available to support their use. Case reports and case report series are the only source of data. As a consequence, they should be administered with caution.

In summary, it is possible to conclude that the identified literature had given us a good insight into IRIS in its general form. IRIS will have the greatest impact in resource-poor countries, where patients are often co-infected with TB and TB drug resistance is rising. To increase the evidence on this topic studies with larger cohorts of patients are needed, and all researchers should use the same diagnostic criteria. Research efforts should focus on diagnosis and treatment of IRIS.

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REVIEW

# The hypothalamus-pituitary-thyroid axis in critical illness

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## ABSTRACT

**The thyroid axis is comprised of thyrotropin-releasing hormone (TRH) at the level of the hypothalamus which stimulates the pituitary to release thyrotropin (TSH). TSH in turn stimulates the thyroid to secrete the pro-hormone thyroxin ($T_4$) and to a lesser extent the receptor active hormone tri-iodothyronine ($T_3$). The majority of circulating $T_3$ is generated by peripheral conversion of $T_4$ by the intracellular iodothyronine deiodinases. Thyroid hormone (TH) is transported over the cell membrane by specific TH transporters such as monocarboxylate transporter 8 (MCT8). After transport and metabolisation in the cell, $T_3$ can interact with nuclear TH receptors and activate or inactivate TH responsive genes.**

**Critically ill patients show uniform disturbances in the hypothalamus-pituitary-thyroid axis. There is clear evidence that circulating and tissue TH levels are low and this is called the low $T_3$ syndrome or non-thyroidal illness syndrome. The clinical importance of the low $T_3$ syndrome is still not very clear because it can either protect against or aggravate the catabolic state. Recently, novel insights were generated into the pathophysiology of the low $T_3$ syndrome. Recent studies in animal models as well as in patients have shown alterations in TH transport and also in deiodinase activity which, together, may suggest an attempt of certain peripheral tissues as well as of the hypothalamus to compensate for low circulating TH levels. Reduced expression of TRH in the hypothalamus appears to play a key role in the prolonged phase of critical illness, although the processes that trigger this upstream disturbance remain unclear.**

## KEYWORDS

Deiodinase, critical illness, hypothalamic TRH, low $T_3$ syndrome, MCT8, TSH

## CRITICAL ILLNESS

Critical illness is a condition in which patients depend on intensive medical support of vital organ functions in order to survive. Interestingly, studies have shown that the acute phase and chronic phase of critical illness are very different in terms of the metabolic and endocrine responses.[1] In the initial phase, these metabolic adaptations result in an increased availability of glucose, free fatty acids and amino acids as substrates for vital organs such as the immune system and the brain.[2,3]

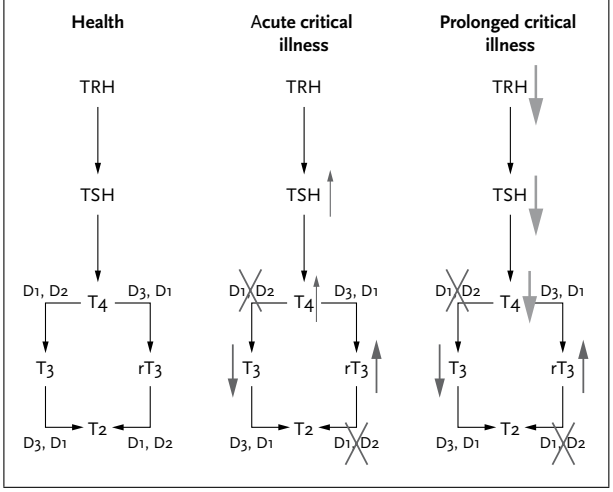
These changes have consistently been considered to be adaptive and beneficial, as they may postpone anabolism and, at the same time, activate the immune response.[4] In prolonged critical illness, a so-called 'wasting syndrome' occurs: despite feeding, protein continues to be lost from vital organs and tissues due to both activated degradation and suppressed synthesis, whereas adipose tissue is preferentially maintained.[5,6] This protein wasting leads to muscle atrophy and weakness, resulting in prolonged dependency on mechanical ventilation. Mortality of prolonged critical illness remains very high, in general exceeding 20%.

In the last decade, many efforts have been made to further understand the neuroendocrine characteristics of critical illness and it has appeared that the acute phase is mainly characterised by an actively secreting anterior pituitary gland and a peripheral inactivation or inactivity of anabolic hormones, whereas prolonged critical illness is hallmarked by reduced neuroendocrine stimulation of target endocrine organs.[7-9] While this has been documented for all hypothalamic-pituitary-dependent axes, the focus of this review will be on the alterations within the thyroid axis.

## LOW $T_3$ SYNDROME

During health, the hypothalamus-pituitary-thyroid (HPT) axis functions as a classical feedback system (*figure 1*). At the level of the hypothalamus, thyrotropin-releasing

**Figure 1.** *Schematic outline of thyroid axis during health, acute critical illness and prolonged critical illness*




hormone (TRH) is released which stimulates the pituitary to secrete thyroid-stimulating hormone (thyrotropin or TSH). TSH in turn drives the thyroid gland to release the prohormone thyroxin ($T_4$) into the circulation. Conversion of $T_4$ in peripheral tissues produces the active hormone 3,5,3'-tri-iodothyronine ($T_3$) and reverse $T_3$ ($rT_3$) which is thought to be metabolically inactive. $T_4$ and $T_3$ in turn exert a negative feedback control on the level of the hypothalamus and the pituitary.

Acute stress, due to sepsis, surgery, myocardial infarction or trauma, causes a drop in circulating $T_3$ levels and a rise in $rT_3$ levels and these changes can already be observed within a few hours after the onset of stress (*figure 1*).[10] Concomitantly, there is a brief rise in circulating levels of $T_4$ and TSH.[11] The changes in the thyroid axis during acute critical illness are so uniformly present in all types of acute illnesses that they have been interpreted as a beneficial and adaptive response that does not warrant intervention.[4,12]

In prolonged critically ill patients circulating $T_3$ levels decrease even further and $T_4$ levels start to decline as well.[8] Despite the low serum $T_3$, and in severe cases also low $T_4$, single-sample TSH levels do not rise but remain within the normal range (*table 1*)[8] suggesting that in the chronic phase of critical illness, patients develop an additional neuroendocrine dysfunction (*figure 1*). It is unlikely that nature has been able to select coping mechanisms for the chronic phase of critical illness. Indeed, survival of this condition has only recently been made possible due to the development of highly technological interventions, making it unlikely that the hormonal responses that co-occur necessarily represent an adaptive response selected by 'nature'. This raises the question whether the low circulating $T_3$ levels are protective in the prolonged phase of critical illness, or rather contribute to the clinical problems and are therefore harmful. To date, however, no studies have shown a benefit in treating patients with thyroid hormone with non-thyroidal illness, including preterm infants and postcardiac surgery patients.[13-19]

Together, these complex alterations that occur within the thyroid axis during critical illness are commonly referred to as the 'euthyroid sick syndrome', 'low $T_3$ syndrome' or 'non-thyroidal illness' (NTI) syndrome,[20] different names indicating the ignorance regarding the exact pathophysiology and on the existence of altered thyroid hormone action as well as the clinical relevance of these changes. In routine clinical care, discrimination between true hypothyroidism and low $T_3$ syndrome or NTI, is difficult but observing the full spectrum of changes in thyroid hormone and TSH levels can help (*table 1*).

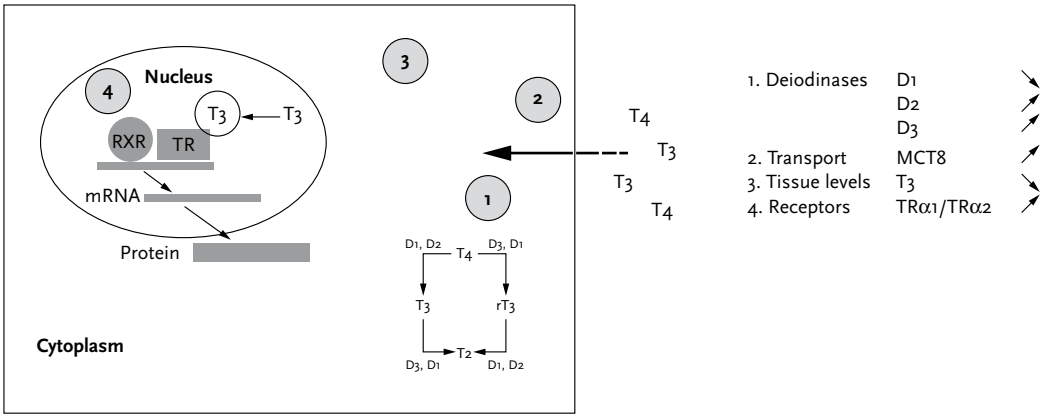
## PERIPHERAL CHANGES WITHIN THE THYROID AXIS DURING CRITICAL ILLNESS

Although thyroid hormone can exert some rapid nongenomic actions, mainly on the heart,[21,22] the major effects are produced by interaction of the active thyroid hormone $T_3$ with nuclear receptors in order to stimulate or inhibit transcription of thyroid hormone responsive genes.[23,24] First, however, thyroid hormone has to be transported over the cell membrane[25] and once inside the cell, it can be metabolised by the iodothyronine deiodinases.[26] Peripheral transport, metabolism and receptor binding of thyroid hormones are all essential steps for normal thyroid hormone action. Changes have been documented in all these steps of thyroid hormone action in the peripheral tissues of critically ill patients (*figure 2*).[26-32] In prolonged

**Table 1.** *Simplified scheme of alterations in thyroid hormone parameters in primary hypothyroidism, central hypothyroidism and non-thyroidal illness*

| | Primary hypothyroidism | Central hypothyroidism | Non-thyroidal illness |
|---|---|---|---|
| $T_4$ | Low | Low | Normal or low |
| $T_3$ | Low or low-normal | Low or low-normal | Low |
| $rT_3$ | Low or normal | Low or normal | Elevated or normal |
| TSH: | | | |
| • Single sample | Elevated | Low or normal | Normal |
| • Pulsatile secretion | Elevated | Low | Low |

**Figure 2.** *Schematic outline of thyroid hormone uptake and metabolism in the cell (left) and overview of the observed peripheral changes in prolonged critical illness (right)*




**TR = thyroid hormone receptor; RXR = retinoid-X receptor; MCT8 = monocarboxylate transporter 8; D1 = type 1 deiodinase; D2 = type 2 deiodinase; D3 = type 3 deiodinase.**

critical illness, these peripheral alterations persist, but a neuroendocrine-induced suppression of thyroidal T4 release, becomes the predominating feature.[1]

**Thyroid hormone deiodination**

There are three types of iodothyronine deiodinases (D1 to D3).[26] These enzymes constitute a family of selenoproteins that selectively remove iodide from T4 and its derivatives thereby activating or inactivating these hormones. In general, each enzyme is expressed in a given cell type. D1 is expressed in the thyroid gland, liver, kidney and pituitary and has outer ring deiodination (ORD) activity, hereby contributing to the bioactivation of T4 to T3, but this enzyme also has inner ring deiodination (IRD) activity especially towards sulphated T4 and T3. D1 activity is regulated by T3 at the transcriptional level which results in a stimulation of D1 activity during hyperthyroidism and a decrease in D1 activity during hypothyroidism.[24] D2 is expressed in the brain, thyroid gland, skeletal muscle and anterior pituitary and only has ORD activity. D2 thus converts T4 into the active hormone T3 and rT3 into 3,3'-diiodothyronine (T2). D2 is thought to contribute to circulating T3[33] and is essential for local T3 production, especially in brain and pituitary.[34] D3 only has IRD activity and therefore mediates the degradation of thyroid hormone: it catalyses the conversion of T4 into rT3 and of T3 into T2.[26,35] It is present in brain, skin, various foetal tissues, and in pregnant uterus and placenta where it protects the foetus against excess T3 concentrations, which are detrimental for normal development.[36] It has been named an oncofoetal protein since it has also been found in vascular tumours and malignant cell lines.[32] These D3-expressing tumours cause a massive inactivation of circulating thyroid hormone which leads to a condition called 'consumptive hypothyroidism'.[37]

During critical illness, the changes observed in circulating thyroid hormone parameters, i.e. low T3 and high rT3, suggest that decreased monodeiodination of T4 could be involved.[18,19] This would result in reduced conversion of T4 into active T3 and increased metabolisation of T4 into the inactive metabolite rT3. This was indeed confirmed in a study by Peeters *et al.* who showed that D1 activity is markedly reduced in post-mortem liver samples of critically ill patients as compared with values previously observed in healthy individuals.[20] Furthermore, D1 activity correlated positively with the serum T3/rT3 ratio, the latter being associated with the degree of tissue hypoperfusion preceding death in these patients.[20] Decreased hepatic D1 expression and activity is likely mediated by cytokines as shown in a mouse model of acute illness and in primary cultures of rat hepatocytes.[25-27] Debaveye *et al.* were able to demonstrate in a unique rabbit model of prolonged critical illness that the drop in D1 activity is reversible as it can be reactivated by infusing TRH in critically ill rabbits.[21,28] This treatment restored hepatic D1 activity and brought serum T4 and T3 levels back within normal range.[21] Since D1 is also important for degradation of sulphated iodothyronines, it was hypothesised that sulphated T4 (T4S) could be increased in critically ill patients who have a diminished D1 activity. The concentrations of sulphated iodothyronines in serum are normally low[38,39] and indeed, in one study, increased circulating concentrations of T4S were measured in critically ill patients as compared with healthy references.[40] A negative correlation was found between serum T4S levels and D1 activity in the liver suggesting that a decreased liver D1 activity could play an important role in the increase of T4S levels during critical illness. However, analysis of serum T4S levels in children with meningococcal sepsis has led to different results. In these children, average T4S levels were decreased as compared with healthy controls.[41]

D3 is normally absent in adult tissue but Peeters *et al.* showed a reactivation of D3 in liver and muscle of critically ill patients.[31] In a rabbit model of prolonged critical illness, D3 activity could be suppressed when T3 levels were increased either by the continuous infusion of TRH in combination with a growth hormone (GH) secretagogue or by the administration of growth hormone.[28] Together, the reduction in D1 and reactivation of D3 result in a decreased activation and an increased inactivation of thyroid hormone in critically ill patients.[31]

D2 activity is controlled by thyroid status both at the pre- and post-translational level: D2 is upregulated during hypothyroidism, whereas high T3 levels will lead to diminished D2 activity.[26] These characteristics make D2 an ideal player for regulating local T3 levels, which has been demonstrated clearly in the rat brain.[42,43] Surprisingly, a report by Larsen *et al.'s* group showed that skeletal muscle D2 may significantly contribute to circulating T3 as well, particularly in the hypothyroid state.[33] The investigators therefore suggested that diminished D2 activity during critical illness could play a key role in the reduced activation of T4 into T3 in that condition. In contrast to this hypothesis, however, our research group found increased levels of D2 gene expression and activity in skeletal muscle of prolonged but not acute critically ill patients.[29] These findings were not explained by changes in circulating cortisol, cytokines or by altered organ function. The data suggest that at least in the prolonged phase of critical illness, D2 adapts appropriately to the low T3 levels, and likely does not contribute to the 'low T3 syndrome' in this condition

**Thyroid hormone binding and transport**

The majority of T3 and T4 in serum is bound to thyroid hormone-binding proteins such as T4-binding globulin (TBG), transthyretin (TTR) and albumin.[44] During health, approximately 0.03% of the total serum T4, and 0.3% of the total serum T3 are present in free or unbound form and it is only this free fraction that is available for transport across the cell membrane.[45,46] In acute events such as sepsis or coronary bypass surgery it has been shown that circulating levels of T4-binding proteins are low, which contributes to the decreased serum T4 levels.[41,47,48] Also, studies suggest that in the serum of critically ill patients, disease-specific inhibitors of thyroid hormone binding may be present.[49,50] This could potentially result in diminished uptake of thyroid hormone by cells or in a distortion of the normal interaction between thyroid hormone and its nuclear receptors. This was shown by adding serum of critically ill patients to cultured hepatocytes which inhibited the uptake of T4 into these cells.[51-53] This has led to the identification of several inhibitors, such as indoxyl sulphate, nonesterified fatty acids, and bilirubin which circulate in increased concentrations during critical illness.[51,54] However, a study by Brent and Hershman showed that exogenous T4 administration to prolonged critically ill patients could restore circulating T4 back to normal levels. Therefore, an inhibitor of binding cannot be the predominate cause of low serum T4 during critical illness.[15]

During critical illness, T4 uptake in the liver is decreased which can also contribute to lowered T3 production.[55,56] Possibly, this can be explained by an existing negative energy balance leading to hepatic adenosine-5'-triphosphate (ATP) depletion.[57,58] This idea is supported by the observation that administration of fructose to healthy volunteers, transiently decreasing liver ATP levels, was followed by a temporary decrease in liver T4 uptake.[59]

Recently, it was shown that gene expression of the very specific thyroid hormone transporters MCT8 is upregulated in liver and skeletal muscle of prolonged critically ill patients. This coincided with a significant inverse correlation between circulating thyroid hormone parameters and MCT8 gene expression in skeletal muscle.[30] This means that patients with the lowest serum T3 and T4 levels show the highest upregulation of MCT8 mRNA. Furthermore, in a rabbit model of prolonged critical illness, treatment with a combination of T3 and T4, thereby increasing circulating levels of T3 and T4, reduced transporter expression levels in liver and skeletal muscle.[30] This shows that in this animal model, thyroid hormone transporter expression levels are regulated by the thyroid hormone status during critical illness resulting in increased MCT8 expression levels when circulating and tissue iodothyronine levels are low and a decrease in MCT8 expression when circulating and tissue iodothyronine levels are high. These data suggest that some tissues may try to adapt to the low circulating T3 levels by increasing expression of thyroid hormone transporters in order to facilitate cellular uptake of thyroid hormone.

**Thyroid hormone tissue levels**

There are many studies showing that circulating iodothyronine levels are reduced during critical illness,[60-63] but only a few attempted to measure iodothyronine concentrations in tissues. Peeters *et al.* showed that there is a good correlation between circulating T3 levels and skeletal muscle as well as liver T3 content in critically ill patients.[64] In this study, the investigators also showed that in patients who had received thyroid hormone treatment, serum T3 concentrations were higher with concomitantly and proportionally higher skeletal muscle T3 concentrations.[64] This confirmed the findings of Arem *et al.* who showed that, in general, T3 concentrations were decreased in the tissues of patients who died after prolonged critical illness, as compared with the levels observed in tissues obtained from patients who died suddenly from a car accident.[65] This suggests that low circulating iodothyronine levels actually result in hypothyroidism at tissue level during critical

illness. However, the bioactivity of thyroid hormone is not only dependent on its concentration in the cell; it can also be modulated at the level of its nuclear receptors. There are three functional thyroid hormone receptors: TRα1, TRβ1 and TRβ2 and they all bind T3 with similar affinity.[66,67] The TRs bind to thyroid hormone response elements in specific target genes which are then transcriptionally activated or repressed. In the absence of thyroid hormone, TRs repress or silence basal transcription of positively regulated genes in proportion to the amount of receptor and the affinity of receptor binding sites.[68] Of special interest is TRα2, which is also encoded by the TRα gene. It lacks a functional ligand binding domain and acts as a dominant negative inhibitor of thyroid hormone action.[69] A study by Thijssen-Timmer *et al*. showed that the TRα1/TRα2 ratio in postmortem liver biopsies from critically ill patients was inversely related to the T3/rT3 ratio.[32] Also, sicker and older patients showed higher TRα1/TRα2 ratios as compared with the less sick and younger ones. Increasing the expression of the active form of the thyroid hormone receptor gene could be a mechanism to enhance sensitivity to T3 in the oldest and sickest patients and can be regarded as an adaptive response to decreasing levels of circulating thyroid hormone.

## NEUROENDOCRINE CHANGES DURING CRITICAL ILLNESS

In addition to the peripheral changes in thyroid hormone metabolism, critical illness is hallmarked by some very distinct neuroendocrine alterations that are quite different in the prolonged phase of critical illness as compared with the first few hours or days after the onset of a severe illness.[70] In the acute phase of critical illness, circulating T3 levels drop which is followed by a brief rise in serum TSH concentrations. TSH levels subsequently return to normal levels despite ongoing decline in T3 levels.[8,11] But the nocturnal TSH surge that is present in healthy individuals is shown to be absent in these patients.[11] The fact that TSH levels remain relatively normal in face of declining T3 concentrations can be indicative of an altered set-point for feedback inhibition within the hypothalamic-pituitary-thyroid axis.[8,11]

In the prolonged phase of critical illness, TSH secretion loses its pulsatility and this loss of pulsatility is positively correlated to the low serum levels of T3.[8,9] When patients start to recover from their illness, an increase in serum TSH can be observed.[71,72] In the hypothalamus, TRH gene expression is also shown to be dramatically reduced in patients dying after chronic critical illness as compared with those who died after a road accident or an acute illness.[73] Furthermore, a positive correlation is shown between TRH mRNA levels and serum T3.[73] These findings indicate that the reduced production of thyroid hormones in the prolonged phase of critical illness may have a neuroendocrine origin. This is further substantiated by the finding that a continuous infusion of TRH can increase TSH secretion and, concomitantly, increase the low circulating levels of T4 and T3 back into the normal ranges.[9] This suggests a predominantly central origin of the suppressed thyroid axis in prolonged critical illness.

### Role of cytokines

Cytokines have been investigated as putative mediators of the acute low T3 syndrome.[74-77] Mice were injected with tumour necrosis factor-α (TNFα), interleukin (IL)-1, IL-6 or IFNγ, but only IL1 was able to induce a systemic illness.[74] Despite this systemic illness, serum T3, T4 and TSH levels were unchanged. Only IFNγ decreased serum T4 and T3 in a dose-dependent manner without changes in serum TSH.[74] Studies in humans on the other hand showed a relation between IL-6 levels and serum T3 values[78] and when TNFα was injected in healthy male subjects, changes in circulating thyroid hormone levels were observed that were reminiscent of the low T3 syndrome.[77] On the other hand, there are several arguments against a causative role of cytokines in directly evoking the low T3 syndrome. Cytokine antagonism for example failed to restore normal thyroid function both in humans[79] and in animal studies.[80] And in a large group of hospitalised patients, cytokines were not withheld as independent determinants of the variability in circulating T3.[75]

### TRH feedback in the hypothalamus

One of the marked features in prolonged critical illness is the suppressed TRH gene expression in the hypothalamus in the face of low circulating thyroid hormone levels. Several mechanisms have been proposed for the suppression of the HPT axis during critical illness, among which a local thyrotoxicosis in the hypothalamus. Increased hypothalamic T3 availability, despite low circulating T3 levels, could indeed explain feedback inhibition of the TRH gene in the context of the low T3 syndrome. One way to increase the local concentration of T3 in the hypothalamus is by increased local conversion of T4 to T3. More than 80% of T3 in the brain originates from local T4 to T3 conversion by D2.[42] Therefore, an upregulation of D2 in the mediobasal hypothalamus could lead to a local hyperthyroid state which in turn would suppress TRH in hypophysiotropic neurons. This has recently been shown in a study of prolonged critically ill rabbits.[81] Injection of LPS in rats and mice has also shown to upregulate hypothalamic D2 expression and activity.[27,82,83] This effect did not seem to be induced by hypothyroidism[84] but could be a direct effect of induced cytokines on D2 expressing tanycytes.[85,86] Alternatively, decreased inactivation of T3 and T4 by D3 could also lead to higher hypothalamic thyroid

hormone levels suppressing TRH. In line with this, a mouse model for chronic inflammation showed decreased D3 mRNA expression in the region of the hypothalamic paraventricular nucleus.[87] Another possible mechanism, by which local iodothyronine levels in the hypothalamus could be increased, is elevated transport of iodothyronines into the hypothalamus. Study of MCT8 null-mice suggests that its expression is necessary for normal feedback regulation of hypophysiotropic TRH neurons.[88,89] Recently, in a rabbit model of prolonged critical illness, upregulation of other thyroid hormone transporters, MCT10 and OATP1C1, was documented.[81]

Although increased local T3 availability in the hypothalamus could explain reduced TRH expression by feedback inhibition, there is one report of a study in critically ill patients wherein thyroid hormone content was measured in the hypothalamus. In this study, hypothalami from critically ill patients contained less than half the concentration of T3 as compared with patients who died from an acute trauma.[65] Also in the rabbit model of prolonged critical illness, T3 content in the hypothalamus was not increased.[81] Therefore, other possible mechanisms driving the suppression of TRH expression and release in the context of critical illness should be considered and investigated. In the presence of such suppressors, the alterations observed in D2 and in thyroid hormone transporters during prolonged critical illness could be interpreted as a compensatory response.

**Feedback by neuronal afferents**

TRH neurons in the PVN also receive input from the melanocortin signalling system which consists of at least two antagonising neuron populations located in the arcuate nucleus of the hypothalamus. One group of neurons synthesise alpha melanocyte stimulating hormone (α-MSH) and co-express cocaine and amphetamine-regulated transcript (CART), while the other group of neurons synthesise neuropeptide Y (NPY) and co-express agouti-related peptide (AGRP). The α-MSH neurons have an activating, while NPY neurons have an inhibiting effect on TRH expression.[90] Interestingly, the action of these two neuron populations is also modulated by leptin, a hormone produced by adipocytes, which declines in the fasting state and returns to normal levels by refeeding. The changes in serum thyroid hormones and TSH during fasting could be the result of declining leptin levels which results in an inhibition of α-MSH production and increased AGRP production.[91,92] In critical illness however, the mechanisms for reducing TRH seem to be different. Endotoxin administration in rodents, which simulates infection, increases rather than decreases α-MSH gene expression and does not alter the expression of NPY in arcuate nucleus neurons.[93] Furthermore, in patients who died from severe illness, NPY expression was reduced and showed a positive correlation with TRH levels[90] while an inverse correlation was seen during starvation.[88]

## THERAPEUTIC INTERVENTIONS

Although circulating thyroid hormone levels are inarguably low during critical illness, there is no consensus on the potential role for thyroid hormone treatment in this patient group. The clinical studies with T4 or T3 administration have failed to demonstrate important clinical benefit in critically ill patients.[15,94] These studies have several limitations, however. Firstly, they were not well powered to detect clinically significant changes. Secondly, it could be argued that, with a rise in D3 and reduced D1, T4 is not an appropriate therapy due to the preferential conversion of T4 to rT3 rather than to T3. Also, prolonged infusion of T3 alone is not ideal, as this will hold risk of suppression of endogenous T4 production, due to feedback inhibition. Theoretically, this could evoke hypothyroidism at the time of interruption of the T3 treatment. Brief administration of substitution doses of T3 after cardiac surgery in paediatric patients has been shown to improve postoperative cardiac function[14] and very brief, merely intraoperative, T3 treatment in adult cardiac surgery patients provided acute haemodynamic improvements, without detectable longer-term clinical benefits.[16] The paediatric patients in the study mentioned above, however, were treated with dopamine which induces iatrogenic hypothyroidism and therefore that study does not provide hard evidence of clinical benefit with treatment of the non-iatrogenic low T3 syndrome of prolonged critical illness.[95,96] Several other frequently used ICU drugs can also affect the HPT axis (*table 2*). Whether these drugs induce an iatrogenic suppression of the HPT axis, such as clearly shown with dopamine infusion, is not well documented. Furthermore, it remains unclear whether iatrogenic hypothyroidism

**Table 2.** *Frequently used ICU drugs interfering with thyroid hormone economy*

| |
|---|
| Glucocorticoides |
| Iodinated contrast agents, iodine wound dressings |
| Propranolol |
| Amiodarone |
| Barbiturates |
| Dopamine |
| Opiates |
| Benzodiazepines |
| Sulphonamides |
| Somatostatin |
| Furosemide |

adversely affects outcome. One population in which such a risk for adverse outcome can be inferred and thus dopamine treatment should be avoided is the neonates, as the importance of adequate thyroid function for neurocognitive development is beyond debate.

Alternatively, treatment with hypothalamic releasing peptides may be a better strategy. Studies by our group have shown that TRH infusion in critically ill patients could reactivate the thyroid axis.[9] Interestingly, when TRH is co-infused with GH secretagogues a rise in circulating rT3 is avoided.[9] Experiments in rabbits have further shown that infusion of TRH with GH secretagogues could reduce D3 activity and increase hepatic D1 activity.[28] In addition, the negative feedback exerted by thyroid hormones on the level of the pituitary is maintained, avoiding unnecessary overstimulation of the thyroid axis,[97] making it a potentially safer treatment than the administration of T3. The clinical outcome benefit of combined TRH and GH secretagogue-induced stimulation of the thyroid axis in prolonged critical illness remains to be investigated.

## NOTE

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ORIGINAL ARTICLE

# Prognostic value of cardiac troponin I in patients with COPD acute exacerbation

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## ABSTRACT

**Background: Chronic obstructive pulmonary disease (COPD) is frequently associated with right ventricular loading and pulmonary hypertension. We aimed to evaluate a possible association between cardiac troponin I (cTnI) levels and adverse events in hospitalised patients with acute exacerbation of COPD.**

**Methods: Retrospective cohort study, with analysis of admissions for acute exacerbation of COPD, with cTnI obtained in the first 48 hours of admission. A positive cTnI test was defined as 0.012 ng/ml or higher (99th percentile). Baseline and peak troponin I levels were taken as independent variables, and outcome variables included length of hospital stay, complications during hospitalisation, and in-hospital and extra-hospital mortality (evaluated 18 months post-discharge).**

**Results: Data concerned 173 patients (105 male, 68 female), with a median age of 77 years (interquartile range of 11 years). The median baseline cTnI was 0.030 ng/ml (n=173), and the median peak cTnI was 0.040 ng/ml (n=173; absolute peak value of 1.260 ng/ml). Nearly 70% of cases had a positive cTnI at admission. Both baseline and peak cTnI correlated significantly with the need for noninvasive ventilatory support. We were not able to find significant differences in in-hospital survival associated with the two troponin groups, but overall 18-month survival was significantly higher among patients with lower values of baseline and peak cTnI.**

**Conclusions: In patients hospitalised for acute COPD exacerbations, elevated baseline and peak cTnI were associated with a greater need for noninvasive ventilatory support and were significant predictors of 18-month overall survival.**

## KEYWORDS

COPD, survival, troponin

## INTRODUCTION

At present, elevation of plasma cardiac troponin I (cTnI), a biomarker highly specific for myocardial muscle, is a major criterion in the diagnosis of myocardial infarction.[1,2] Nonetheless, the development of cTnI measurement assays has made it possible to study plasma levels amongst the general population, without myocardial ischaemia or necrosis. Increased values of cTnI have been seen in a number of other conditions, including left ventricular hypertrophy, chronic renal insufficiency, diabetes, heart failure and pulmonary embolism.[3,4] Whereas increased troponin I plasma values in the setting of heart failure probably originate in the left heart, in pulmonary embolism the right chambers constitute the probable source for the release of troponin into the circulation.

Chronic obstructive pulmonary disease (COPD) is a lung disease characterised mainly by airflow limitation that is not fully reversible,[5] and corresponds to the major cause of chronic respiratory insufficiency and Cor pulmonale. Cor pulmonale can be defined as right ventricular enlargement (hypertrophy and/or dilatation), caused by pulmonary artery hypertension resulting from diseases affecting the structure and/or function of the lungs, which may, in time, lead to right ventricular failure.[6]

During acute exacerbations, COPD patients, whether or not with a history of Cor pulmonale, have an increased cardiac burden, as stated by Currie *et al.*[7] Therefore, there may be a release of cTnI in these circumstances, and this could have prognostic implications. In fact, Baillard *et al.*, studying a cohort of 71 patients with COPD acute exacerbations, found elevated troponin I values to be a strong predictor of in-hospital death.[8] Higher in-hospital mortality was also seen among heart failure patients with increased plasma troponin levels.[9] Additionally, Harvey *et al.*[10] noted that serum troponins are commonly raised in acute exacerbations of COPD

and appear to reflect the severity of the exacerbation. More recently, Brekke *et al*. studied 897 patients with COPD exacerbation and verified that patients with elevated troponin T levels were at increased risk of death after discharge.[11]

Noninvasive ventilatory support (NIVS) is a crucial strategy in treating the most severe acute COPD exacerbations.[12] In this setting, release of cTnI at presentation, possibly reflecting cardiac strain resulting from respiratory insufficiency, may be an important predictor of patients who will require more aggressive treatment, such as NIVS.

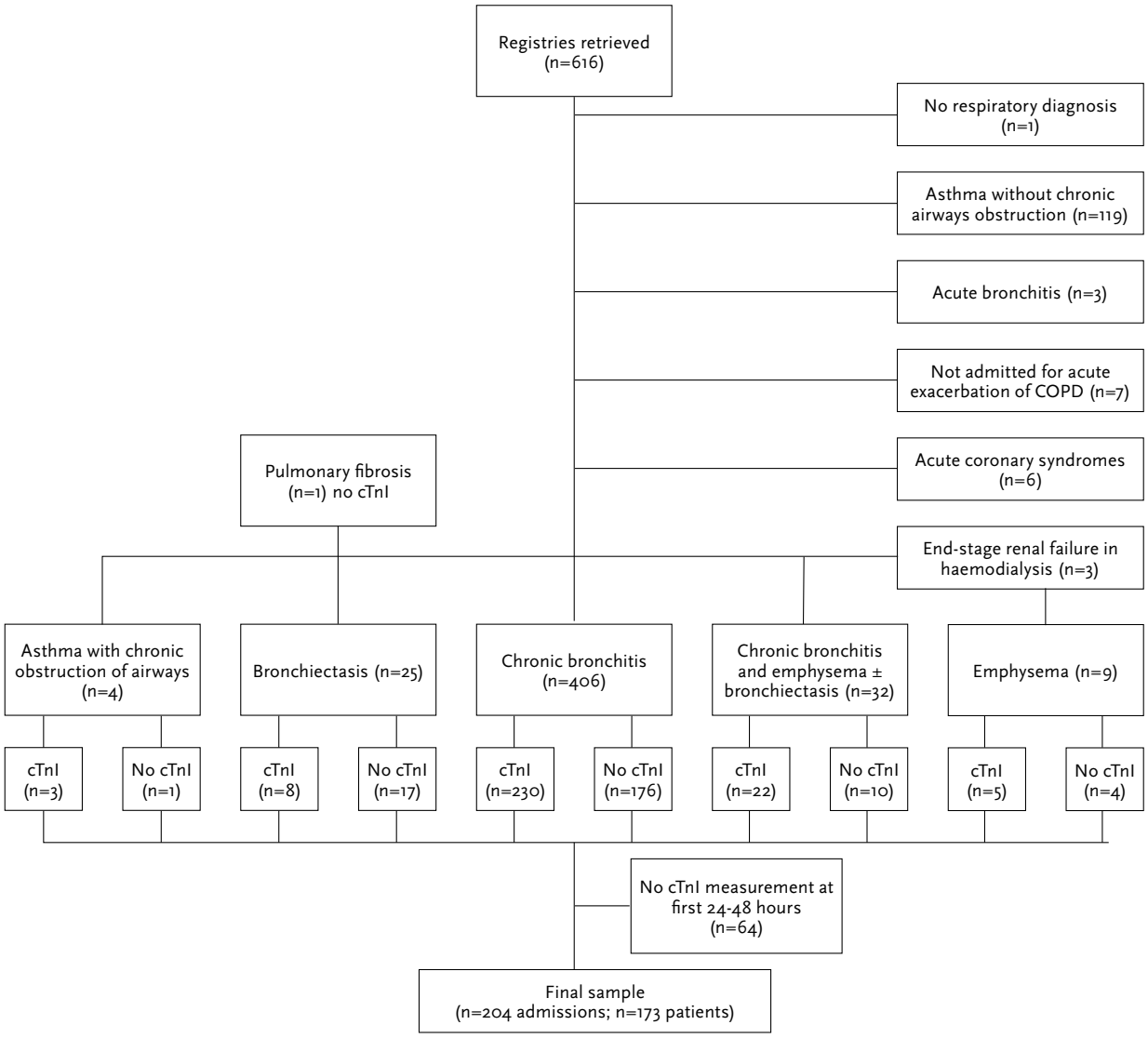
The aims of the present study were to ascertain the range of cTnI values during acute exacerbations of COPD, and evaluate their prognostic implications, namely on mortality and need for NIVS.

## METHODS

The present report consists of a retrospective cohort study, which was approved by the institutional ethics board of São João Hospital, Porto, Portugal (*figure 1*). Given the nature of the study, written informed consent was not considered necessary. Nevertheless, verbal consent was obtained from a sample of patients interviewed by means of telephone calls, in which the patients were informed about the study's aim and were asked some questions.

The initial study population consisted of all patients older than 18 years, consecutively admitted for acute exacerbation of COPD to the Department of Internal Medicine of a central university hospital, throughout the year 2007. From this population, we selected the patients who had cardiac

**Figure 1.** *Flowchart describing a retrospective cohort study involving 173 patients with acute exacerbation of chronic obstructive pulmonary disease*




**N = number; cTnI = cardiac troponin I.**

troponin I measurement at presentation. Exclusion criteria included marked renal failure (estimated glomerular filtration rate <15 ml/min),[13] persistent haemodynamic instability requiring inotropic or vasoactive support, pulmonary embolism, myocardial infarction and cardiac arrest before admission. All diagnoses were made by the attending physician.

Cases were identified by consulting the electronic records for all admissions to the hospital during the year 2007, with primary discharge coding diagnosis of COPD exacerbation. We retrospectively collected demographic, clinical and analytical data. Missing data were completed by telephone interviews. Demographics included information about gender, ethnic group, age and job. Clinical data incorporated symptoms and signs at admission, comorbidities (particularly obesity, arterial hypertension, ischaemic heart disease, previous myocardial infarction, atrial fibrillation, diabetes, tobacco use), apparent cause of exacerbation, results of standard diagnostic procedures (arterial blood gas (ABG), chest X-ray and electrocardiogram; whenever available, lung function tests and echocardiography), length of hospital stay, and in-hospital complications. Analytical data comprised haematological (globular volume, haemoglobin) and plasma biochemical parameters (cTnI, natriuretic peptide type B (BNP), MB fraction of creatine kinase (CK MB), myoglobin, C-reactive protein, creatinine, sodium and potassium). We considered cTnI measured at baseline (first measurement) and peak troponin level (maximum value recorded during hospitalisation). For patients with more than one admission, we used data concerning only the first admission.

At least 18 months after discharge from hospital, all patients with available contact numbers were contacted by telephone in order to ascertain their vital status and after-discharge intercurrences.

COPD definition fulfilled the ICD-9 classification, and COPD acute exacerbation was ascertained by certifying an increase in cough and dyspnoea, as well as a change in sputum abundance and purulence. Cor pulmonale conformed to the Weitzenblum criteria.[6] Other diagnoses were determined by the attending/discharging physician as documented in the medical records. The severity of COPD exacerbations was evaluated by clinical (altered level of consciousness, signs of respiratory rate exceeding 25 breaths/min, paradoxical abdominal breathing, ineffective cough) and ABG (while breathing room air, arterial oxygen pressure lower than 50 mmHg and blood pH below 7.35) criteria, as stated in medical records. Baseline and peak values of cardiac troponin I were taken as independent variables. For comparison of categorical outcome variables incidence according to both troponin values, we considered them to be categorical variables. For that reason, both baseline and peak cTnI were each categorised in two classes according to the 99th percentile of the cTnI assay available in our hospital: 1) ≤0.012 ng/ml; 2) >0.012 ng/ml. BNP determination, when available, was also included in the calculations. Outcome variables included length of hospital stay, overall complications during hospitalisation, need of NIVS, in-hospital and 18-month post-discharge extra-hospital mortality. The first variable was treated as a continuous variable, and the others as dichotomous categorical variables.

**Cardiac troponin I measurement assay**

cTnI and BNP measurements were made by means of chemiluminescence's microparticle immunoassay, using the ARCHITECT STAT system, of Abbott Diagnostics (Abbott Park, Illinois, USA). The analytical sensitivity of this cTnI assay was demonstrated to be at ≤0.010 ng/ml, with a 95% confidence level. The 99th percentile of troponin I in a normal population with this assay was established at 0.012 ng/ml. Therefore, all values above this threshold were taken as positive.

**Statistical analysis**

Continuous variables were presented as median and interquartile range, and categorical variables as absolute and relative frequencies. Univariate comparison of continuous data was performed using the Mann-Whitney U test. Categorical variables were compared using a $\chi^2$ test or Fisher's exact test as appropriate. The correlations between BNP and both baseline and peak cTnI were determined using Pearson's test, and their significance assessed by Kruskal-Wallis test. The correlation of baseline and peak cTnI and length of hospital stay was assessed by simple linear regression, and for that purpose we performed a logarithmic transformation of the independent and dependent variables, as their distributions were asymmetrically positive.

In-hospital and 18-month survival curves were determined using Kaplan-Meier estimates, and were compared between groups (negative *vs* positive) of both baseline and peak cTnI by the log-rank test. To account for baseline covariates, Cox-proportional hazards survival modelling was used. Covariates included gender, age, creatinine and BNP.

For all comparisons a two-sided p value of 0.05 was considered statistically significant. Data analysis was performed using the SPSS 16.0 software programme.

## RESULTS

We retrieved 616 registries of admissions with main discharging diagnosis of chronic obstructive pulmonary disease (COPD) and related conditions (codes 490 to 496 of ICD-9), of which 123 were primarily excluded since the patients did not have chronic airways obstruction (119 with

asthma without chronic airways obstruction, three with acute bronchitis, and one with no respiratory diagnosis at all). After analysis of the medical records, we additionally excluded 16 cases (seven were not admitted for acute exacerbation of COPD, six had acute coronary syndromes, and three had end-stage renal disease on haemodialysis). Cardiac troponin I (cTnI) was only ordered in about 56% (n=268) of the remaining 477 admissions confirmed to be COPD with acute exacerbations. For the purpose of our study we considered only those patients who had a first cTnI measured at no more than 48 hours after admission, therefore attaining a final sample of 204 reports, corresponding to 173 patients, whose baseline characteristics are depicted at *table 1*.

Patients had a median age of 77 years (interquartile range of 11 years), with male predominance (105 male, 68 female). Chronic bronchitis was the main diagnosis related to COPD, and previous Cor pulmonale was only seen in 17 cases. Previous medical conditions did not vary significantly in relation to sex, but women were clearly more prone to using β-blockers and diuretics, and men, domiciliary oxygen supplementation (*table 1*).

The median cTnI of the first serum determination was 0.030 ng/ml (n=173), and the median value of peak cTnI was 0.040 ng/ml (n=173; absolute peak value of 1.260 ng/ml). *Tables 2* and *3* summarise the results, according to baseline and peak cTnI categories. Nearly 70% of the patients with COPD who presented to the emergency room with acute exacerbations had positive results of cTnI in the first 48 hours after admission.

The patients with cTnI >99th percentile were significantly older, and in agreement with previous reports, more often had a previous history of congestive heart failure, chronic renal failure and atrial fibrillation or flutter. In addition, they were more likely to have higher values of natriuretic peptide type B (BNP), and also attained higher values of peak cTnI during hospital stay (*table 2*).

BNP was available in only 149 patients. The median of BNP serum determination was 268.4 ng/ml (interquartile

**Table 1.** *Baseline characteristics of 173 chronic obstructive pulmonary disease (COPD) patients admitted for acute exacerbations*

| | Males, n (%) 105 (60.7) | Females, n (%) 68 (39.3) | P value |
|---|---|---|---|
| Age, median (interquartile range) | 75.0 (11) | 78.5 (9.5) | 0.012 |
| COPD, n (%) | | | |
| • Chronic bronchitis | 90 (85.7) | 66 (97.1) | 0.140 |
| • Emphysema | 25 (23.8) | 6 (8.8) | 0.011 |
| • Bronchiectasis | 16 (15.2) | 10 (14.7) | 0.822 |
| Known history of Cor pulmonale, n (%) | 12 (11.4) | 5 (7.4) | 0.367 |
| Comorbidities, n (%) | | | |
| • Hypertension | 58 (55.2) | 48 (70.6) | 0.074 |
| • Diabetes | 29 (27.6) | 28 (41.2) | 0.201 |
| • AF/AFlt | 38 (36.2) | 26 (38.2) | 0.612 |
| • Chronic heart failure | 47 (44.8) | 41 (60.3) | 0.077 |
| • Ischaemic heart disease | 23 (21.9) | 19 (27.9) | 0.465 |
| • Chronic renal failure | 18 (17.1) | 11 (16.2) | 0.876 |
| • Obesity | 20 (19.0) | 20 (29.4) | 0.292 |
| • Dyslipidaemia | 34 (32.4) | 31 (45.6) | 0.262 |
| • Cerebral vascular disease | 18 (17.1) | 13 (19.1) | 0.741 |
| Chronic medication, n (%) | | | |
| • ACEIs | 38 (36.2) | 30 (44.1) | 0.298 |
| • ARBs | 9 (8.6) | 11 (16.2) | 0.132 |
| • Antiplatelets | 33 (31.4) | 26 (38.2) | 0.357 |
| • β-blockers | 6 (5.7) | 11 (16.2) | 0.030 |
| • CCBs | 12 (11.4) | 8 (11.8) | 0.946 |
| • Digitalic | 15 (14.3) | 16 (23.5) | 0.125 |
| • Diuretics | 55 (52.4) | 47 (69.1) | 0.030 |
| • Hypolipidemic drugs | 32 (30.5) | 21 (30.9) | 0.955 |
| • Nitrates | 15 (14.3) | 11 (16.2) | 0.734 |
| • Domiciliary oxygen | 54 (51.4) | 24 (35.3) | 0.038 |
| Hospital stay length (days), median (interquartile range) | 10 (6) | 9 (4.8) | 0.238 |
| Laboratory data, median (interquartile range) | | | |
| • Baseline cTnI | 0.030 (0.065) | 0.026 (0.046) | 0.263 |
| • Peak cTnI | 0.040 (0.093) | 0.031 (0.064) | 0.552 |
| • CRP | 36.6 (96.3) | 19.1 (57.6) | 0.027 |
| • Creatinine | 1.10 (0.51) | 0.94 (0.36) | 0.003 |
| • BNP | 246.1 (524.6) (n=83) | 275.3 (455.4) (n=66) | 0.829 |

**N = number; p = probability; AF = atrial fibrillation; Aflt = atrial flutter; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; cTnI = cardiac troponin I; peak cTnI = maximum value for cTnI; CRP = C-reactive protein; BNP = natriuretic peptide type B.**

**Table 2.** *Data as obtained in 173 chronic obstructive pulmonary disease (COPD) patients admitted for acute exacerbations, according to baseline cTnI categories*

| | cTnI ≤0.012 ng/ml (n=52) | cTnI >0.012 ng/ml (n=121) | P value |
|---|---|---|---|
| Age, years, median (interquartile range) | 74 (12.3) | 78 (9) | 0.001 |
| Sex, n (%) | | | |
| • Female | 22 (42.3) | 46 (38.0) | 0.596 |
| • Male | 30 (57.7) | 75 (62.0) | |
| Peak cTnI, ng/ml, median (interquartile range) | 0.010 (0.002) | 0.060 (0.100) | 0.000 |
| Creatinine, mg/dl, median (interquartile range) | 0.90 (0.38) | 1.05 (0.52) | 0.011 |
| BNP, pg/ml, median (interquartile range) | 131.75 (216.1) (n=46) | 322.20 (621.7) (n=103) | 0.000 |
| Hospital stay length, days, median (interquartile range) | 8 (5) | 11 (6) | 0.014 |
| In-hospital mortality, n (%), median (interquartile range) | 2 (3.9) | 9 (7.4) | 0.383 |
| Noninvasive ventilatory support, n (%) | 12 (23.1) | 54 (44.6) | 0.009 |
| Comorbidities, n (%) | | | |
| • Hypertension | 31 (59.6) | 75 (62.0) | 0.618 |
| • Diabetes | 14 (26.9) | 41 (33.9) | 0.314 |
| • AF/AFlt | 11 (21.2) | 53 (43.8) | 0.004 |
| • Chronic heart failure | 22 (42.3) | 69 (57.0) | 0.054 |
| • Ischaemic heart disease | 10 (19.2) | 33 (27.3) | 0.229 |
| • Chronic renal failure | 5 (9.6) | 23 (19.0) | 0.117 |
| • Obesity | 11 (21.2) | 27 (22.3) | 0.798 |
| • Dyslipidaemia | 18 (34.6) | 48 (39.7) | 0.452 |
| • Cerebral vascular disease | 13 (25) | 17 (14.0) | 0.101 |

**N = number; p = probability; cTnI = cardiac troponin I; peak cTnI = maximum value for cTnI; AF = atrial fibrillation; Aflt = atrial flutter; BNP = natriuretic peptide type B.**

**Table 3.** *Data as obtained in 173 chronic obstructive pulmonary disease (COPD) patients admitted for acute exacerbations, according to maximum cTnI categories*

| | Peak CTnI ≤0.012 ng/ml (n=42) | Peak CTnI >0.012 ng/ml (n=131) | P value |
|---|---|---|---|
| Age, years, median (interquartile range) | 74 (10) | 78 (10) | 0.001 |
| Sex, n (%) | | | |
| • Female | 15 (35.7) | 53 (40.5) | 0.584 |
| • Male | 27 (64.3) | 78 (59.5) | |
| Baseline cTnI, ng/ml, median (interquartile range) | 0.010 (0) | 0.040 (0.062) | 0.000 |
| Creatinine, mg/dl, median (interquartile range) | 0.91 (0.39) | 1.04 (0.48) | 0.102 |
| BNP, pg/ml, median (interquartile range) | 114.75 (219.01) | 308.60 (585.10) | 0.000 |
| Hospital stay length, days, median (interquartile range) | 8 (5) | 10 (6) | 0.005 |
| In-hospital mortality, n (%) | 1 (2.4) | 10 (7.6) | 0.252 |
| Noninvasive ventilatory support, n (%) | 7 (16.7) | 59 (45.0) | 0.020 |
| Comorbidities, n (%) | | | |
| • Hypertension | 25 (59.5) | 81 (61.8) | 0.789 |
| • Diabetes | 11 (26.2) | 44 (33.6) | 0.372 |
| • AF/AFlt | 8 (19.04) | 56 (42.7) | 0.007 |
| • Chronic heart failure | 18 (42.9) | 73 (55.7) | 0.148 |
| • Ischaemic heart disease | 8 (19.1) | 35 (26.7) | 0.319 |
| • Chronic renal failure | 5 (11.9) | 23 (17.6) | 0.390 |
| • Obesity | 9 (21.4) | 29 (22.1) | 0.923 |
| • Dyslipidaemia | 14 (33.3) | 52 (39.7) | 0.461 |
| • Cerebral vascular disease | 8 (19.0) | 22 (16.8) | 0.737 |

**N = number; p = probability; cTnI = cardiac troponin I; peak cTnI = maximum value for cTnI; AF = atrial fibrillation; Aflt = atrial flutter; BNP = natriuretic peptide type B.**

range = 482.1 ng/ml). Baseline and peak cTnI values were significantly correlated with one another (r=0.74, p<0.001). Conversely, neither showed any significant correlation with BNP (r=0.06, p=0.438 and r=0.07, p=0.430 for baseline and peak cTnI, respectively). As depicted in *table 4*, the larger proportion of patients had BNP levels between 100 and 500 pg/ml. Kruskal-Wallis test demonstrated that median peak troponin (but not baseline cTnI) varied significantly (p=0.031) among the BNP categories.

**Table 4.** *Data as measured in a subset of 149 chronic obstructive pulmonary disease (COPD) patients admitted for acute exacerbations*

| | BNP categories | | | |
|---|---|---|---|---|
| | ≤100 pg/ml | 100.01-499.99 pg/ml | ≥500 pg/ml | Total |
| Baseline cTnI ≤0.012 ng/ml | 16 | 18 | 11 | 45 |
| Baseline cTnI >0.012 ng/ml (a) | 20 | 51 | 33 | 104 |
| Peak cTnI ≤0.012 ng/ml | 13 | 13 | 10 | 36 |
| Peak cTnI >0.012 ng/ml (b) | 23 | 56 | 34 | 113 |
| *Total* | *36* | *69* | *44* | *149* |

**Patients were divided by natriuretic peptide type B (BNP) levels, according to cardiac troponin I (cTnI), either baseline (top) or peak value (bottom). (a) Probability of 0.057 *vs* patients with baseline cTnI ≤0.012 ng/ml, Kruskal-Wallis test; (b) probability of 0.031 *vs* patients with peak cTnI ≤0.012 ng/ml, Kruskal-Wallis test.**

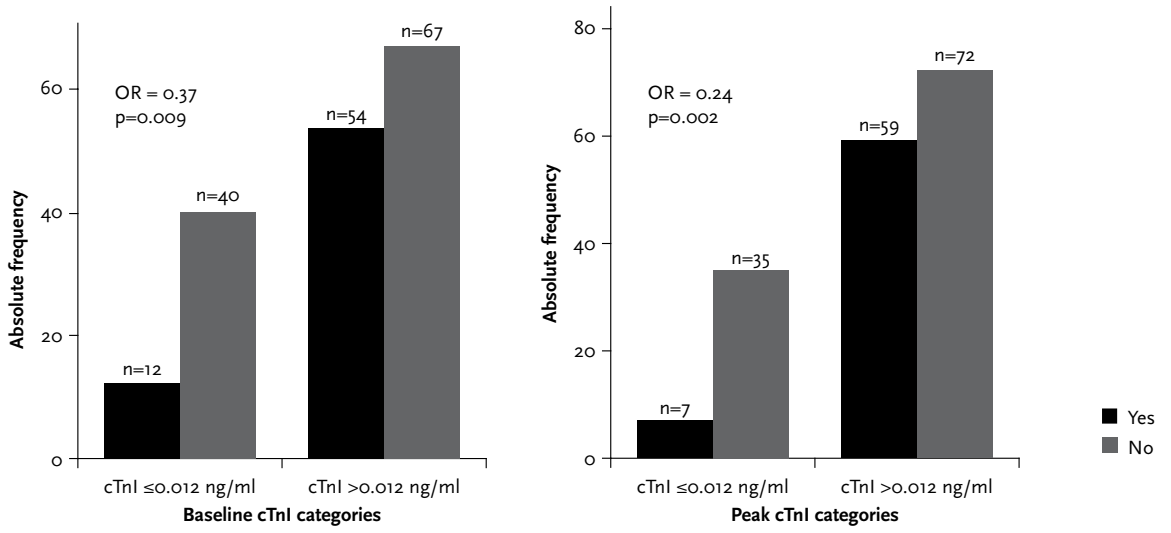
Length of hospital stay differed significantly when comparing both baseline (p=0.014) and peak cTnI (0.005) in the two patient groups (negative/positive). Nonetheless, when applying the linear regression method, only peak cTnI predicted (p=0.046) the hospitalisation period.

Overall complications were significantly correlated with cTnI at admission; they were less likely to occur (OR=0.397) if the cTnI was under the 99th percentile (p=0.007). The same relation was observed with peak cTnI (OR=0.344, p=0.005). Requirement of noninvasive ventilatory support was the main complication, occurring in nearly 38% of patients (n=66). We found that patients had a 63% lower probability (p=0.009) of requiring noninvasive ventilatory support if they had basal cTnI values under 0.012 ng/ml (*figure 2*). Noninvasive ventilatory support requirement also differed significantly according to the peak cTnI categories (OR=0.24, p=0.002). As shown in *figure 2*, patients with lower levels of peak cTnI had a 76% lower probability of needing that type of ventilation.

The in-hospital death rate was 5.9%. Vital status at discharge did not vary significantly according to either baseline or peak cTnI. Kaplan-Meier survival analysis did not show any significant differences in overall in-hospital survival, whether the patients first cTnI measurement was positive or negative. The same holds true for peak cTnI. Controlling for sex, age, BNP and creatinine, Cox regression analysis did not demonstrate any statistically significant differences in terms of in-hospital survival either.

Data concerning 18-month survival could not be obtained for 13 patients, whose records did not include a valid telephone number. The 18-month post-discharge death rate was 21.1%. In contrast to the data concerning in-hospital

**Figure 2.** *Distribution of patients in terms of need for noninvasive ventilatory support (NIVS), according to baseline and peak cardiac troponin I (cTnI) categories, using the Mantel-Haenszel common odds ratio estimation**




***From a cohort of 173 chronic obstructive pulmonary disease (COPD) patients admitted for acute exacerbations.**
**The probability of requiring noninvasive ventilatory support was significantly higher in patients with either baseline or peak cTnI above 0.012ng/ml. N = number; OR = odds ratio; p = probability.**

survival, overall 18-month survival analysis revealed a statistically significant difference (p=0.007) when comparing patients who had a baseline cTnI lower than the 99th percentile to those in the other group (*figure 3*). Identical to baseline cTnI, peak cTnI also predicted overall 18-month survival (p=0.012). Moreover, by means of Cox regression analysis, adjusting for the same variables, it was shown that overall survival continued to be significantly higher (p=0.030) among those patients with negative initial cTnI. A similar finding was observed with peak cTnI (p=0.021).

## DISCUSSION

In the present study, about 70% of patients with COPD acute exacerbations had a positive cTnI at presentation. It has been shown previously that patients with COPD encompass a great prevalence of cardiovascular diseases,[15] mainly chronic heart failure and pulmonary embolism, but also ischaemic heart disease. In this cohort, according to the retrospective character, the diagnoses were made by the attending/discharging physician, posing a problem in terms of accurate exclusion of all those comorbidities known to raise cardiac troponin.

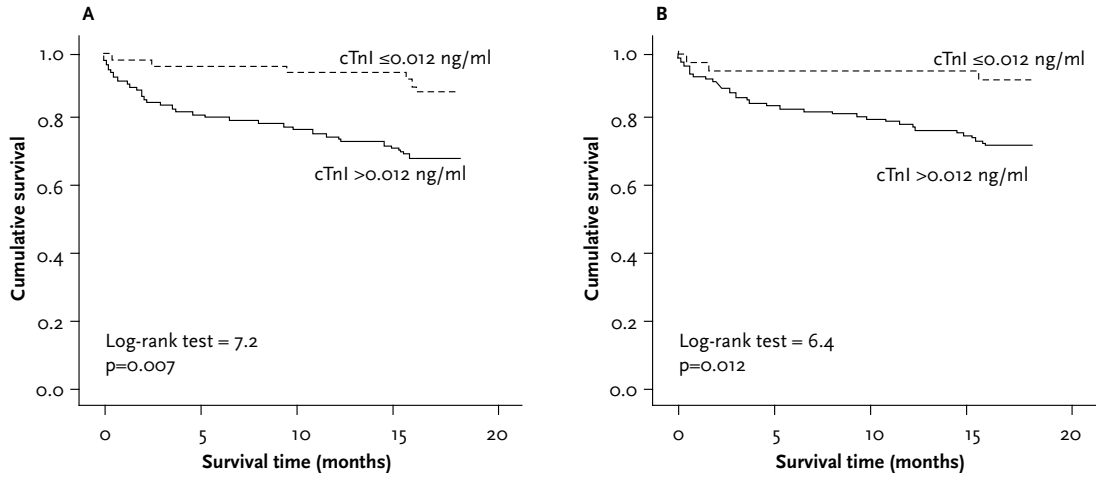
Regarding interpretation of small increases of cardiac troponin, mostly in patients with nonischaemic heart disease, many studies have been carried out during the last decade. Initially, increased plasma levels of cardiac troponin I were presumed to be due to myocardial necrosis, as happens in myocardial infarction. Antman *et al*. studied a group of 1404 patients with acute coronary syndrome and found a higher mortality rate in patients with increased values of plasma cardiac troponin I.[2] Moreover, increased values of plasma cardiac troponins (either I or T) were found in a number of other clinical situations, including heart failure and sepsis.[16,17] Pulmonary embolism is also a relatively frequent cause of increased plasma troponin.[18] In the case of pulmonary embolism, myocardial necrosis is not a prominent phenomenon, and right ventricular strain could be the cause of troponin release.[19] COPD patients could have a similar mechanism for troponin release as pulmonary embolism patients, since right ventricular overload is a prominent phenomenon in this condition.

Hessel *et al*. showed that in the presence of compounds that stimulate stretch-responsive integrins, viable cardiomyocytes release intact cardiac troponin I.[20] Previous work by Feng *et al*. had shown preload, rather than ischaemia, to induce troponin I degradation.[21] COPD patients frequently have hypoxia, and thus the hypothesis that hypoxia also plays a role in troponin release in COPD patients cannot be ruled out.

Peacock *et al*. studied troponin levels in 84,872 patients with heart failure, and found higher in-hospital mortality in patients with elevated troponin levels.[9] In COPD patients, both Baillard *et al*.[8] and Brekke *et al*.[11] found troponin levels to correlate with certain outcomes – in-hospital death and death after discharge, respectively. The present results are in good agreement with these latter findings.

It seems important to account for heart failure (whether overt or overlooked) when dealing with COPD patients presenting for an acute exacerbation. In fact, it was recently demonstrated that left ventricular dysfunction is closely related to COPD acute exacerbations.[22,23] BNP has a

**Figure 3.** *Kaplan-Meier survival analysis of 160 chronic obstructive pulmonary disease (COPD) patients admitted for acute exacerbations, comparing baseline cardiac troponin I (cTnI) values (A) and peak cTnI levels (B)*




**The overall 18-month mortality was significantly higher in cTnI-positive when compared with cTnI-negative patients (probability = 0.007 and 0.012, respectively). p = probability.**

negative predictive value for heart failure when under 100 pg/ml and is strongly in favour of left ventricular failure when above 500 pg/ml.[22] However, increased BNP has been seen in mitral stenosis, a disease in which the left ventricle is unaffected.[24]

As stated previously, in the present study, patients who had positive cardiac troponin I were older, had higher BNP values, more often had a history of congestive heart failure and atrial fibrillation/flutter. In addition, cardiac troponin I values, either positive or negative, varied significantly among BNP classes. Myocardial strain could be an important cause of troponin release in these patients. As the majority of patients had BNP levels between 100 and 500 pg/ml, cardiac troponin may result from right ventricular dysfunction, from moderate left ventricular failure, or from both.

The overall in-hospital complications were found to be significantly higher among patients with either baseline cTnI or peak cTnI plasma levels above the 99th percentile. These patients were also more prone to have longer hospital stays, leading to the hypothesis that those complications could be related to hospital stay.

Patients with either baseline cTnI or peak cTnI plasma levels ≥0.012 ng/ml were more likely to require noninvasive ventilatory support. According to this finding, we might add hypoxaemia as a contributing factor for troponin release, as well as subsequent myocardial strain (perhaps also because of tachycardia).

Both Baillard *et al.*[8] and Brekke *et al.*[11] found troponin levels to correlate with in-hospital death and death after discharge, respectively. Consistent with this, our study demonstrated significantly higher odds of dying during the first 18 months after discharge amongst patients with elevated cTnI at presentation or at peak level. Patients with elevated cTnI had a higher prevalence of both heart and renal failure; these diseases are in their own right predictors of survival, and this could contribute to our findings.

**Study limitations**

As the present report derives from a retrospective study, data were ascertained from past records, possibly leading to information bias; in addition, the outcomes (hospital stay length, in-hospital complications, in-hospital survival and survival after discharge) were evaluated at a later date. However, the outcomes chosen are objective parameters. Bias from nonresponse and losses to follow-up were seen in what concerns the 18-month mortality data (13 patients). Lack of control for possible independent variables may have occurred, namely concerning the fact that cTnI was measured only in 56% of acute COPD exacerbations. Given these limitations, it would be better to have the conclusions of the present report confirmed by other studies.

## CONCLUSIONS

The present study showed that a great proportion of patients hospitalised for acute exacerbations of COPD have levels of cTnI above the 99th percentile. Both left ventricular and right ventricular dysfunction could be implicated as sources of cTnI release in this context.

Noninvasive ventilatory support requirement was significantly more likely to occur among patients with elevated cTnI (≥0.012 ng/ml – 99th percentile), when compared with those patients with lower levels. Elevated levels of both baseline and peak cTnI were also found to be significant predictors of 18-month overall survival.

## NOTE

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CASE REPORT

# Takotsubo cardiomyopathy following radioiodine therapy for toxic multinodular goitre

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## ABSTRACT

**We report on a 73-year-old man with a toxic multinodular goitre, which was treated with radioiodine therapy (I-131) without pretreatment with an antithyroid drug. Four weeks later he presented with rapidly progressive dyspnoea and a significant increase in free thyroxin. The electrocardiogram showed ST-segment elevation, and echocardiography demonstrated apical akinesia and a left ventricular ejection fraction of only 25%. However, direct coronary catheterisation showed no evidence of coronary artery disease. Left ventricular angiography showed apical ballooning consistent with the diagnosis of takotsubo cardiomyopathy. Following treatment of the cardiomyopathy and thyrotoxicosis, he experienced a complete recovery. To the best of our knowledge, this is the first report of a takotsubo cardiomyopathy associated with thyrotoxicosis resulting from radiation thyroiditis induced by radioiodine. Three other cases of takotsubo cardiomyopathy associated with Graves' disease have been described in literature.**

*What was known on this topic?*
Takotsubo cardiomyopathy consists of reversible left ventricular dysfunction with characteristic apical ballooning, without significant epicardial coronary artery stenosis. It is triggered by an acute medical illness or intense emotional or physical stress. Three cases of takotsubo cardiomyopathy associated with Graves' hyperthyroidism have been reported.

*What does this add?*
To the best of our knowledge, this is the first report of a takotsubo cardiomyopathy provoked by thyrotoxicosis resulting from radiation thyroiditis induced by radioiodine. We suggest determination of thyroid function in all patients with takotsubo cardiomyopathy.

## KEYWORDS

Heart failure, radioiodine therapy, takotsubo cardiomyopathy, toxic multinodular goitre

## INTRODUCTION

Takotsubo cardiomyopathy, also called stress-induced cardiomyopathy, consists of reversible apical or midventricular left ventricular dysfunction with sparing of the basal segments, without significant epicardial coronary artery stenosis. This entity is named after the round-bottomed narrow-necked Japanese fishing pot used for trapping octopus, because of the peculiar left ventricle apical ballooning evident on left ventriculogram. It is typically triggered by an acute medical illness such as sepsis,[1,2] exacerbation of a pre-existing condition, or by intense emotional or physical stress, and predominantly affects women.[3,4] Patients who survive the acute episode typically recover normal ventricular function within one to four weeks. Here, we report a patient with a takotsubo cardiomyopathy associated with thyrotoxicosis resulting from radiation thyroiditis induced by radioiodine.

## CASE REPORT

A 73-year-old man with a history of prostatic carcinoma and toxic multinodular goitre, which was treated with radioiodine therapy (iodine-131) five years ago, was now admitted for rapidly progressive dyspnoea. Four weeks before admission

he was retreated with iodine-131 in another hospital for recurrent hyperthyroidism (free thyroxin (FT4) 34 pmol/l (10 to 22); thyroid-stimulating hormone (TSH) <0.1 mIU/l (0.35 to 5.0)) due to toxic multinodular struma (confirmed by thyroid scintigraphy). There was no preceding treatment with an antithyroid drug. On presentation in the emergency room, he had no chest pain, palpitations, diarrhoea, or change in weight. During the last weeks he had been more easily irritated. His blood pressure was 155/85 mmHg, with a pulse rate of 127 beats/min. An enlarged thyroid with multiple nodules of varying sizes was observed. Examination of the lungs revealed diffuse rales at both bases. Furthermore, he had mild oedema of the lower extremities and fine tremor of the hands. The electrocardiogram showed a sinus tachycardia with ST-segment elevation in the anterior precordial leads and T-wave inversion in the lateral leads (*figure 1A*). His blood tests showed an elevated troponin of 2.92 µg/l (0.00 to 0.10), a depressed TSH of <0.1 mIU/l, and a significant increase in FT4 to 55 pmol/l, probably as a result of radiation thyroiditis by radioiodine. Transthoracic echocardiography (TTE) showed simultaneous apical akinesia and a hyperkinetic basal area with a substantially reduced left ventricular ejection fraction (LVEF) of 25% (*figure 1B-E*). Direct coronary catheterisation showed no evidence of coronary artery disease, but left ventricular angiography revealed apical ballooning consistent with the diagnosis of takotsubo cardiomyopathy.

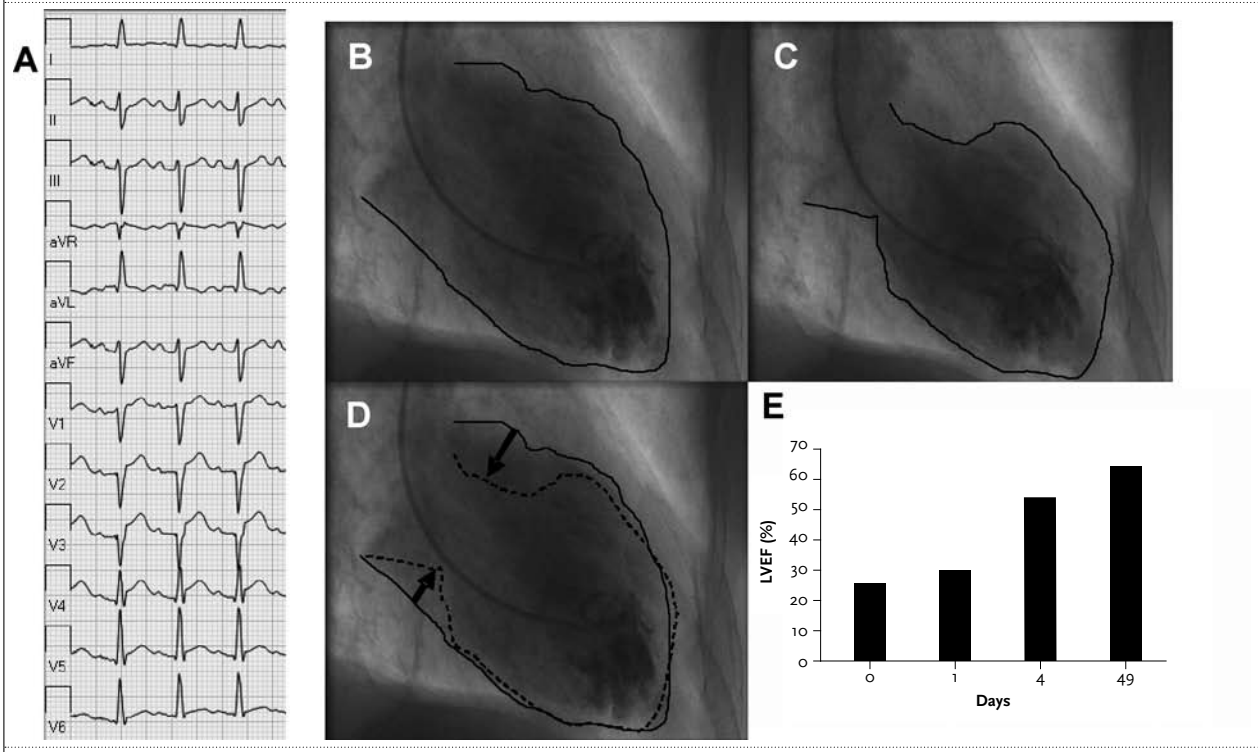
He was treated with diuretics, an angiotensin-converting enzyme inhibitor, and low-molecular-weight heparin. The thyrotoxicosis was treated according to recently published guidelines,[5] with propylthiouracil and hydrocortisone, both inhibitors of the peripheral conversion of thyroxin to triidothyronine. After 24 hours his condition had improved markedly and propranolol was started. Repeat echocardiography after four days showed significant improvement of the LVEF to 57% with only mild hypokinesia of the apical segments (*figure 1E*). Maximal CK release was 201 U/l (0 to 170).

At outpatient follow-up after seven weeks, all cardiac segments had normal contractility and the LVEF was 65% (*figure 1E*). At that time the electrocardiogram had normalised. He experienced a complete recovery with normal activity.

## DISCUSSION

Thyrotoxicosis is associated with an increased risk of atrial fibrillation and the high cardiac output can lead to

**Figure 1.** *Electrocardiogram at presentation showing sinus tachycardia with ST-segment elevation in the anterior precordial leads and T-wave inversion in the lateral leads (A), left ventriculogram at presentation demonstrating apical akinesia of a takotsubo pattern (B-D) and serial echocardiographic assessment of the left ventricular ejection fraction (E)*




**Panel B shows the appearance of the left ventricle during diastole and panel C during systole. In panel D a projection of diastole and systole is shown. Echocardiography was performed on admission; on hospital days 1 and 4; and at outpatient follow-up on day 49.**

worsening of heart failure or angina pectoris.[6,7] In addition, three cases of takotsubo cardiomyopathy associated with Graves' hyperthyroidism have been described in literature.[8-10] To the best of our knowledge, this is the first report of a takotsubo cardiomyopathy provoked by thyrotoxicosis resulting from radiation thyroiditis induced by radioiodine.

The pathogenesis of takotsubo cardiomyopathy is still unclear, but coronary artery spasm, myocarditis, and catecholamine-induced microvascular dysfunction and myocardial toxicity may be involved. The apex may be more vulnerable to sudden catecholamine surges due to greater β-adrenergic receptor density and/or increased myocardial responsiveness to adenylate stimulation.[11] Thyroid hormone modulates the transcription of multiple genes and also has extranuclear action in cardiac myocytes leading to various cardiovascular effects similar to catecholamine-mediated stimulation of β-adrenergic receptors.[7] Evidence that β-adrenergic receptors contribute to the cardiovascular effects of hyperthyroidism includes increased expression of β-adrenergic receptors in thyrotoxicosis and significant improvement of cardiovascular symptoms in thyrotoxicosis by β-blockade. However, a recent study showed that these effects of hyperthyroidism are largely independent of β-adrenergic stimulation.[12]

## CONCLUSION

We present a patient with takotsubo cardiomyopathy following radioiodine therapy for toxic multinodular struma. Pretreatment with an antithyroid drug to deplete thyroid hormone stores before administration of radioiodine could have prevented the thyrotoxicosis and takotsubo cardiomyopathy in this patient. Various signs and symptoms in cardiomyopathy and thyrotoxicosis are similar, which implies that hyperthyroidism in takotsubo cardiomyopathy may be underreported. We suggest determination of thyroid function in all patients presenting with takotsubo cardiomyopathy.

## NOTE

Part of this report was presented as an oral presentation at the Nederlandse Internisten Dagen, 23-4-2009.

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CASE REPORT

# Pulmonary coccidioidomycosis: import illness and the importance of travel history

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## ABSTRACT

**A 35-year-old man presented at the outpatient department of pulmonary diseases with fever, rhinitis and coughing. He had recently been on holiday in California. Except for a body temperature of 39.7°C there were no other abnormal findings at the physical examination. Chest X-ray showed a consolidation in the left upper lobe. Under antibiotic treatment his clinical condition deteriorated. Coccidioidomycosis was the suspected diagnosis and confirmed by the results of CT scanning and culture of bronchoalveolar lavage fluid. Treatment with itraconazole resulted in lasting improvement. The case stipulates the importance of travel history.**

*What was known on this topic?*
Coccidioidomycosis is a fungal infection caused by Coccidioides immitis, leading to pulmonary and systemic symptoms and occasionally even disseminated disease.

*What does this case add?*
An advice to consider the diagnosis of coccidioidomycosis in patients with symptoms of a respiratory tract infection who have recently visited the southwest region of the USA, an endemic area.

## KEYWORDS

Coccidioidomycosis, pneumonia, import illness, itraconazole

## INTRODUCTION

Coccidioidomycosis was first recognised in 1892 as a progressive disfiguring skin disease with organ complications and since 1937 as the cause of an acute respiratory syndrome called valley fever.[1] The fungus *Coccidioides immitis* is endemic in certain areas of Northern and Southern America. Of the estimated 100,000 infections per year in the United States, 50 to 60% are subclinical.[2,3] When diagnosed, the most common clinical presentation is acute or subacute pneumonic illness. Extrapulmonary disease may develop, affecting any possible organ, usually within a year after the initial infection. In case of impaired immunity, for example by cancer, HIV infection or immunosuppressive therapy, the infection may appear months to years after the primary infection.[2,4] The low number of imported cases of coccidioidomycosis in the Netherlands makes recognition of the infection difficult, and emphasises the importance of travel history.[4,5]

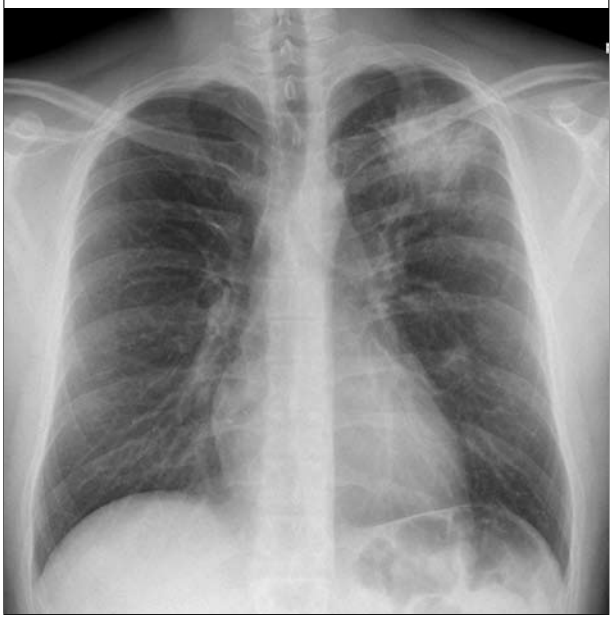
## CASE REPORT

A 35-year-old man presented with flu-like symptoms. He had just spent a three-week holiday in California. The patient's medical history was unremarkable. He was not taking any medications and he did not smoke, drink alcohol or use any illicit drugs. He had a known penicillin allergy.

Before presentation he was treated with azithromycin, which he could not tolerate, followed by cotrimoxazole without any clinical improvement.

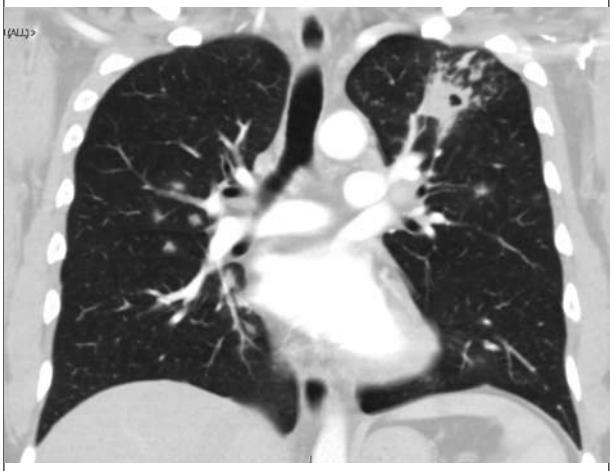
Apart from a fever of 39.7°C, physical examination revealed no abnormalities. Laboratory findings showed an elevated erythrocyte sedimentation rate (49 mm in the first hour) and C-reactive protein (80 mg/l; normal <5 mg/l). No further abnormalities were noted. Chest X-ray showed

**Figure 1.** *Chest X-ray showing a consolidation in the left upper lobe (232 x 241 mm)*



a consolidation in the left upper lobe (*figure 1*). Under the diagnosis of pneumonia caused by *Streptococcus pneumoniae* or an atypical pathogen, he was treated with moxifloxacin. Nevertheless symptoms persisted and the patient was hospitalised for further diagnostics and treatment. A new chest X-ray showed subtle infiltrative lesions in the right lung as well. Intravenous Cefuroxime was added. Because of positive *Chlamydia* serology, moxifloxacin was changed for doxycycline, but only after a diagnostic bronchoscopy with bronchoalveolar lavage (BAL) was done. A tuberculin skin test was negative. Because of persisting fever, prednisone was prescribed and the patient could be discharged on doxycycline and prednisone. However, due to persisting dyspnoea, CT scanning of the thorax was performed, which showed multiple cavitations and fluffy nodules in both lungs (*figure 2*). Meanwhile, serology for HIV, antinuclear factor and antineutrophil cytoplasmatic antigen was negative, as were auramine tests and PCR for tuberculosis, *Chlamydia* and *Mycoplasma* in the BAL fluid. However, the culture for fungi showed growth, and together with the results of the CT scan, coccidioidomycosis was suspected. Treatment with itraconazole was initiated. Later on, *Coccidioides* serology proved to be positive and the cultured fungus was determined as *Coccidioides immitis*. The patient gradually improved under continued treatment with itraconazole.

**Figure 2.** *CT scan showing bilateral nodular pulmonary infiltrates (309 x 237 mm)*



**Note the cavity in the left upper lobe.**

## DISCUSSION

*Coccidioides* species are endemic in certain areas of the southwest of the USA, including the deserts of California, Northern Mexico and several areas in South America. In the Netherlands infections are very rare and mainly found among travellers.[1,5]

Coccidioidomycosis is caused by the dimorphic fungus species *Coccidioides immitis* or *C. posadasii*. The incidence of coccidioidomycosis is increasing, from 21 cases/100,000 in 1997 to 91 cases/100,000 in 2006.[6] Factors that are likely responsible for this increasing incidence include a greater number of persons moving into endemic areas, a growing population with immunosuppression, new constructions in previously undeveloped desert areas and more awareness of this infection among physicians.[1] In the Netherlands roughly ten serologically proven cases are seen each year (Jacques Meis, personal communication).

Coccidioides species grow in the soil of the desert. The lifecycle consists of a mycelial and a spherule phase. The mycelial phase is a mold in the soil growing in hyphae. While maturing, arthroconidia are formed. These arthroconidia may be inhaled and transformed into multinucleated spherical structures. These spherules form internal endospores, which can be released, forming new spherules. If infected material is returned to the soil or if sputum is cultured in the laboratory, mycelia are formed, completing the cycle.[1,2,7]

The incubation period is 7 to 21 days. Approximately 60% of infections occur subclinically. Symptomatic patients may present with symptoms such as coughing, chest pain, fever and fatigue.[1,2,4] Clinically there may be either a subacute process with respiratory and systemic symptoms lasting weeks to months, or an acute process manifesting as a pneumonia. Other symptoms may include arthralgias, and cutaneous manifestations such as erythema nodosum and erythema multiforme.[1,2,4] In the majority of patients clinical symptoms regress spontaneously after several weeks. Occasionally patients have persisting pulmonary lesions in the form of residual nodules or cavities.[1] Disseminated

coccidioidomycosis is estimated to occur in less than 5% of symptomatic patients.[1,2,4] Dissemination may occur months to several years after the primary infection and notably affects skin, lymph nodes and bones. Meningeal disease is less common but also the most feared complication.[1]

Coccidioidomycosis can be diagnosed by a culture from any body fluid, by identifying coccidioidal spherules in cytological smear or biopsy specimen, or by a positive serological test.[1] Serological assays may be compromised in patients with decreased immune response.[4]

In most patients who present with early infectious disease, it will resolve without specific antifungal therapy.[1,3] Nevertheless, management should routinely include repeated patient encounters for one to two years, either to document resolution or to identify pulmonary or extrapulmonary complications.[3] Patients with an immunocompromised status or those who develop progressive pulmonary disease or disseminated disease require antifungal treatment.[1,3] Commonly prescribed therapies include ketoconazole, fluconazole, itraconazole and amphotericin B. The duration of treatment ranges from three to six months, but this may be longer, especially in immunocompromised patients. In case of meningitis, treatment should be continued indefinitely.[3]

## CONCLUSION

In a patient with symptoms of an upper or lower respiratory tract infection and a recent visit to the southwest region of the USA, coccidioidomycosis should be considered. Although usually self-limiting, treatment is indicated in progressive or disseminated disease.

## ACKNOWLEDGEMENT

The authors wish to thank Dr Jacques Meis from the Canisius-Wilhelmina Hospital in Nijmegen, the Netherlands, for his information on the number of coccidioidomycosis infections in the Netherlands.

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PHOTO QUIZ

# A patient with neck pain and fever

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## CASE REPORT

A 40-year-old man without significant medical history presented to the emergency department with a four-day history of neck pain and fever. Two weeks before presentation he had experienced an episode of throat pain with dysphagia and marked lymphadenopathy. There was no recent history of swallowing a foreign body or dental procedures. At presentation, his body temperature was 39.6°C, blood pressure was 140/90 mmHg, pulse rate was 110 beats/min and his respiratory rate was 16 breaths/min. Mild cervical lymphadenopathy was present, as well as local tenderness to gentle percussion of the cervical spine. Intraoral inspection revealed a low-grade periodontitis of element 28 and a red posterior pharyngeal wall, but nasofibroscopy could not demonstrate any swelling of pharyngeal soft tissue, nor were there any signs of oral candidiasis or herpes lesions. On further physical examination normal breath sounds and heart tones were heard, and no skin lesions were observed. On neurological examination there were signs of meningismus, and a diminished biceps reflex on the left side. There was no paresis or sensory deficit present. Cerebrospinal fluid analysis revealed a white blood cell count of 629 cells/mm$^3$. The patient underwent both computed tomography after intravenous contrast, and gadolinium-enhanced MRI of the neck region (*figures 1-3*).

## WHAT IS YOUR DIAGNOSIS?

See page 357 for the answer to this photo quiz.

**Figure 1.** *Sagittal T1-weighted MRI image after gadolinium showing the intraspinal low-signal intensity lesion with wall enhancement at level C5, indicating an intraspinal abscess. Slight swelling and enhancement of the prevertebral soft tissue can also be appreciated*

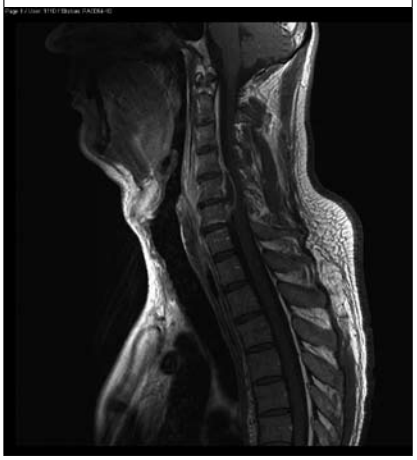


**Figure 2.** *Axial T1-weighted MRI image after gadolinium showing the continuity between the prevertebral compartment and intraspinal compartment of the abscess through the neuroforamen with compression of nerve root C6 on the left. Also notice the anterior displacement and stretching of the longus colli muscle on the left side indicating that the abscess lies in the prevertebral compartment*

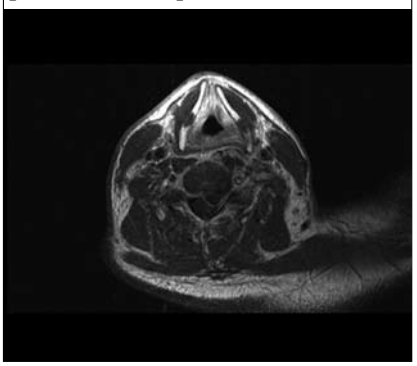
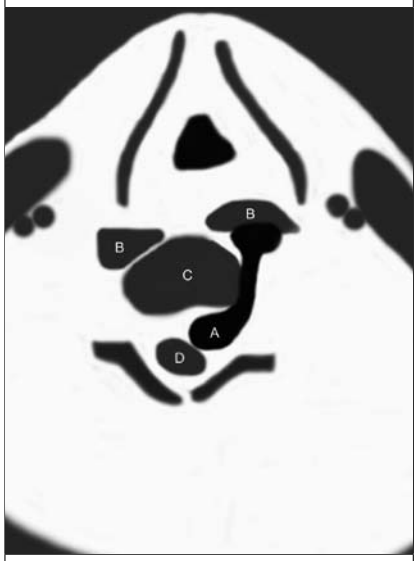


**Figure 3.** *Schematic drawing of the axial T1-weighted MRI image*




**A) combined prevertebral and intraspinal abscess; B) musculus longus colli; C) vertebra cervicalis VI; D) medulla spinalis.**

ANSWER TO PHOTO QUIZ (PAGE 356)

# A PATIENT WITH NECK PAIN AND FEVER

## DIAGNOSIS

Combined prevertebral and intraspinal abscess in a patient with a de novo HIV infection.

The initial CT scan of the neck region raised the suspicion of the presence of an intraspinal abscess. Additional gadolinium-enhanced MRI of the neck region, carried out in order to evaluate the extension of the abscess more accurately, showed a hyperintense lesion on T2-weighted images at C5 to C6 and enhancement of the lesions on the T1 with gadolinium, suggestive of spondylodiscitis. There was also a combined prevertebral and intraspinal abscess over levels C4 to C7 (*figures 1-3*). Gram stain and culture of the cerebral spinal fluid were unremarkable, but blood cultures were positive for *Staphylococcus aureus* (methicilline susceptible). No clues regarding the aetiology of the abscess could be derived from detailed medical history taking (including risk factors for HIV) or the physical examination at the time of initial presentation. Since spinal abscesses could be a rare complication of haematogenous spread of an infective endocarditis, additional transoesophageal echocardiography was performed, but could not reveal any signs indicative of an infective endocarditis.

Nonsurgical treatment of the abscess was initiated with intravenous metronidazole and ceftriaxone, since no paresis or sensory deficit were present at the moment of presentation. After blood culture results became available, treatment was continued with penicillin G 18 x $10^6$ IE/day for six weeks, after which the patient had a complete neurological recovery. Three weeks after neurological recovery however, the patient presented again at the emergency department, this time with a (pneumocystis) pneumonia. Additional immunological studies were performed, which revealed the presence of anti-HIV and p24 antigen, and an HIV-1 RNA level of 912,000 cp/ml (NucliSENS HIV RNA assay (detection limit, 4 x $10^4$ copies/l; Organon Teknika), with a CD4 count of 120/$mm^3$ (normal value 400-1300/$mm^3$), after which retroviral therapy with emtricitabide / tenovovir and efavirens was initiated.

Prevertebral abscesses are a very rare cause (<1%) of deep neck infections.[1,2] They can be discriminated from retropharyngeal abscesses on MRI by looking at the displacement of the longus colli muscle, which is anterior in prevertebral abscesses, and posterior in retropharyngeal abscesses. Deep neck infections are often preceded by odontogenic infections, upper airway infections and skin infections, which can spread either haematogenously or by local extension to the prevertebral space.[3] Predisposing factors that compromise the immune system (such as diabetes mellitus, rheumatoid arthritis, chronic steroid use or (in this case) HIV), render the host more susceptible to the spread of any of these infections to the deep neck space and/or the spinal canal.[4]

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PHOTO QUIZ

# Something fishy

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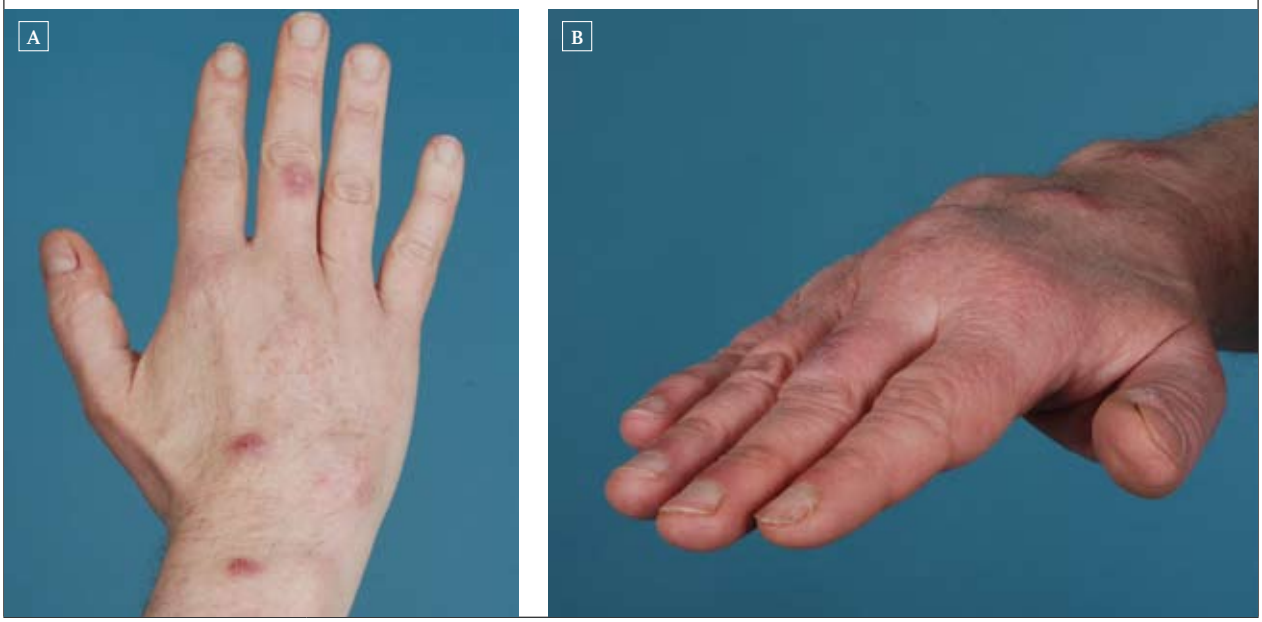
## CASE REPORT

A 57-year-old man with erythematous papulo-nodular lesions on the right hand and right underarm was referred to our hospital by his general practitioner (*figure 1*). At presentation the lesions had been present for approximately six weeks. The patient could remember having a splinter in his right hand prior to the start of the skin symptoms. He worked in the financial department of the city sanitation department, had three cats and a tropical aquarium. There were no relevant comorbidities. The nodules were painful and there was a purulent discharge.

## WHAT IS YOUR DIAGNOSIS?

See page 359 for the answer to this photo quiz.

**Figure 1.** *Erythematous papulo-nodular lesions on the right hand (A) and right underarm (B) with sporotrichoid distribution*



ANSWER TO PHOTO QUIZ (PAGE 358)

SOMETHING FISHY

## DIAGNOSIS

The typical sporotrichoid distribution of these skin lesions in combination with the tropical aquarium that this patient possessed pointed to the diagnosis of 'fish tank granuloma'. The diagnosis was confirmed by positive culture of *Mycobacterium marinum* from the purulent discharge, and a positive polymerase chain reaction of the tissue.

This type of granuloma is caused by infection with *M. marinum*, an atypical *Mycobacterium* that can be found in fresh and salt water. Infection usually occurs through contact with contaminated water from an aquarium, a nonchlorinated swimming pool or otherwise infected water following minor skin trauma.[1] Diagnosis is often delayed because of the rarity of the disease. Differential diagnoses of this type of lesion include sporotrichosis (infection of the skin with the fungus *Sporothrix schenckii*), other mycobacterial infections, *Nocardia brasiliensis* infection, cat scratch disease and *Leishmania braziliensis* infection.[2]

Isolates of *M. marinum* are susceptible to clarithromycin, sulphonamides, tetracyclines, rifampicin and ethambutol. Azithromycin can be used as an alternative to clarithromycin. Guidelines of the American Thoracic Society recommend treatment with two active agents for one to two months after resolution of symptoms, with a typical duration of treatment of three to four months. Susceptibility testing should not be performed routinely, but can be done in cases of treatment failure.[3]

Our patient was successfully treated with azithromycin 500 mg/day and ethambutol 2000 mg/day for five months.

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PHOTO QUIZ

# Yellow-white lesions in the upper gastrointestinal tract

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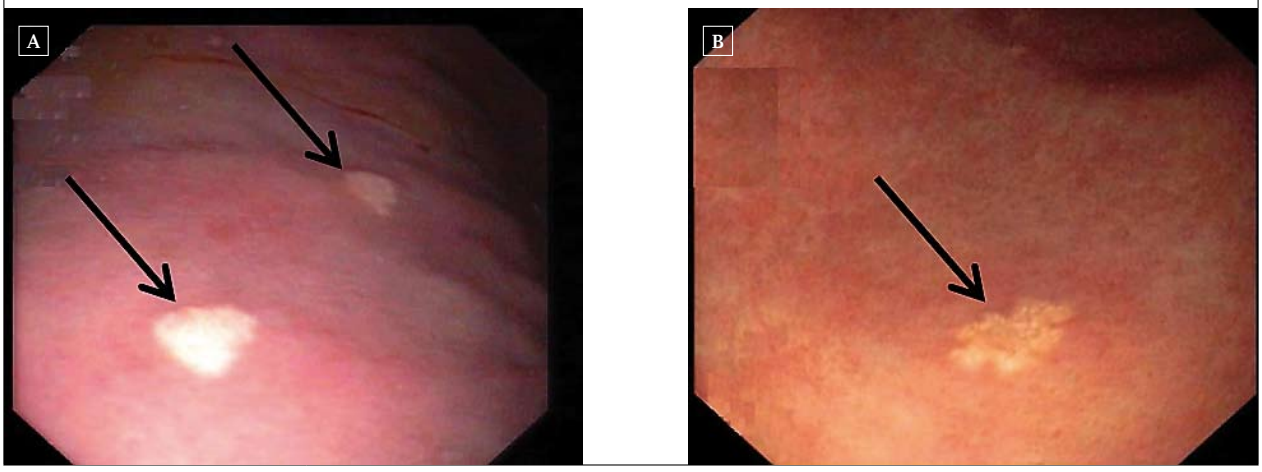
## CASE REPORT

We present two patients who were recently referred to our endoscopy department for upper gastrointestinal (GI) tract endoscopy. In both, we found yellow-white lesions in the stomach during endoscopy. Patient A, a 76-year-old Caucasian male, underwent upper GI tract endoscopy in the work-up of iron deficiency anaemia. His medical history revealed a Billroth-I (B-I) gastrectomy because of a peptic ulcer related perforation. In addition, he had hypertension, angina pectoris and hypercholesterolaemia. Endoscopy showed a normal B-I-anastomosis and multiple yellow-white lesions (diameter 3-4 mm) in the corpus and antrum (*figure 1A*). Patient B, a 72-year-old Caucasian male, underwent upper GI endoscopy because of epigastric pain. He was not on any medication; his medical history was compatible with peptic ulceration and he had undergone previous surgery for gastric volvulus. In 1999, B-cell chronic lymphocytic leukaemia was diagnosed, which was managed conservatively. Endoscopy showed a cascade stomach (i.e. a stomach in which the upper posterior wall is pushed forward, creating an upper portion that fills until sufficient volume is present to spill into the antrum) with similar yellow-white lesions as in patient A in the corpus and cardia (*figure 1B*).

## WHAT IS YOUR DIAGNOSIS?

See page 361 for the answer to this photo quiz.

**Figure 1.** *Endoscopic views of the xanthelasmas (arrows) of patient A (panel A) and patient B (panel B)*



## DIAGNOSIS

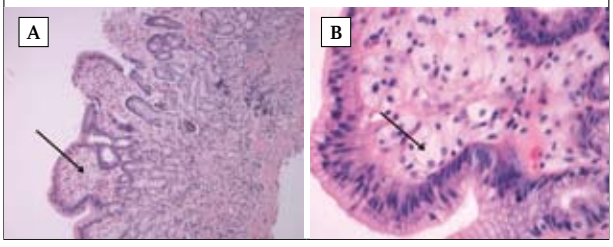
The differential diagnosis at endoscopy included an infectious cause, storage disorders or a rare type of gastric cancer. The histopathological diagnosis of the yellow-white lesions was gastric xanthelasmas. The presence of foamy histiocytes in the lamina propria is the main criterion for the diagnosis (*figure 2*). There were no signs of gastritis or presence of *Helicobacter pylori*.

Xanthelasmas are benign asymptomatic lesions which are incidentally found in the upper GI tract. Gastric xanthelasmas are rare and reported with an incidence of 0.23% within the patients who are subjected to upper GI tract endoscopy.[1] Oesophageal and duodenal xanthelasmas are even more uncommon. In contrast, the prevalence of gastric xanthelasmas in Asia is 7%.[2] Most lesions are described as yellow-white, well-demarcated plaques at endoscopy. The size of the lesions varies from 0.5 to 10 mm in diameter. Although already described by Orth[3] in 1887 as 'lipid-laden macrophages in the gastric mucosa', the aetiology of xanthelasmas still remains unclear. They are likely to be the result of an inflammatory response to mucosal damage, or it may be a consequence of the ageing gastric mucosa.

Xanthelasmas are composed of large foamy cells containing a mixture of lipids, including cholesterol, neutral fat, low-density lipoprotein, and oxidised low-density lipoprotein.[4,5] These cells are mostly histiocytes, although occasionally plasma cells, smooth muscle cells, and Schwann cells participate. In contrast to cutaneous xanthelasmas, there is no evident association between GI xanthelasmas and hyperlipidaemia.[6] It is unknown whether intestinal xanthelasmas are linked to increased cardiovascular risk. Xanthelasmas in the GI tract are benign conditions, but a few case studies have shown early gastric cancer in association with proliferation of xanthoma cells.[7] Furthermore, there is a case description with a clear-cell carcinoid tumour of the stomach, in which the endoscopic and microscopic findings resembled a gastric xanthelasma.[8] Therefore, we recommend that intestinal xanthelasmas are always biopsied in order to achieve an exact histopathological diagnosis. When a patient is diagnosed with upper GI tract xanthelasmas, we do not recommend routine endoscopic follow-up.

In addition, to elucidate the mechanisms of their aetiopathogenesis and to help understand their clinical significance, we would like to invite others to share their experience with gastrointestinal xanthelasmas with us. Therefore please send information about patients and their xanthelasmas to: T.Romkens@MDL.umcn.nl.

**Figure 2.** *Histopathological picture of an xanthelasma (patient A) with patchy aggregates of foamy histiocytes (arrows), haematoxylin and eosin, x 125 (panel A) and x 600 (panel B)*

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