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ORIGINAL ARTICLE

Imported infectious diseases in tertiary hospitals☆

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Abstract
Introduction: An Imported Diseases Clinic was created in the hospital in 2009. The aim of this study was to assess its contribution in terms of capacity, quality of care and teaching offered.
Patients and methods: A retrospective study was conducted from 2009 to 2011, analyzing: (A) development of knowledge by means of protocols and publications created, and subject taught; (B) capacity and quality of care offered by the analysis of patients seen, the adequacy of the protocols and accessibility.

The patients were classified into 3 groups. Group 1: immigrant patient screening, group 2: patient consultation after tropical or sub-tropical travel, group 3: screening of vertical transmission of imported disease.
Results: Six protocols have been developed and disseminated on the unit website, as well as 5 scientific publications. A total of 316 patients were evaluated: 191 included in group 1 (29 Adopted and 162 Immigrants), 57 in group 2 (94.7% Visiting Friends and Relatives and 81.5% without a pre-travel consultation). They consulted due to, gastrointestinal symptoms (52.6%) and fever (43.8%), with 68 included in group 3 at risk of imported disease by vertical transmission (62 *Trypanosoma cruzi*, 1 Human T Lymphotropic Virus and 5 *Plasmodium* spp.). The overall adherence to the protocols was about 77.1%.
Discussion: Infectious Diseases Units must adapt to the reality of the population and be flexible in its structure. Periodic assessment of the quality of care offered is essential, as well as an evaluation on the need for additional studies.

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PALABRAS CLAVE
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Patología infecciosa importada en hospitales terciarios

Resumen
Introducción: En el año 2009 se crea en nuestro centro una Consulta de Patología Importada. El objetivo de este trabajo es conocer su aportación en cuanto a capacidad, calidad asistencial y docencia ofrecida.
Pacientes y métodos: Estudio retrospectivo entre 2009 y 2011 donde se analizan: a) desarrollo del conocimiento mediante la valoración de protocolos y publicaciones realizadas, así como la docencia impartida; y b) capacidad y calidad asistencial ofrecida mediante el análisis de los pacientes atendidos, la adecuación a los protocolos y la accesibilidad a la consulta. Se clasifican los pacientes atendidos en 3 grupos: grupo 1 cribado del paciente inmigrante; grupo 2 consulta tras viaje a zona tropical o subtropical; grupo 3 cribado de enfermedad importada de transmisión vertical.
Resultados: Se han desarrollado y difundido en la web de la unidad 6 protocolos y 5 publicaciones científicas. Se han atendido 316 pacientes: 191 incluidos en el grupo 1 (29 adoptados y 162 inmigrantes); 57 en el grupo 2 (94,7% *Visiting Friends and Relatives* y 81,5% sin consulta previaje), que acudieron principalmente por clínica gastrointestinal (52,6%) y fiebre (43,8%); y 68 en el grupo 3 con riesgo de infección importada de transmisión vertical (62 Trypanosoma cruzi, 1 virus linfotrópico T humano y 5 *Plasmodium* spp.). La adecuación global a los protocolos disponibles fue del 77,1%.
Discusión: Las unidades de patología infecciosa deben adaptarse a la realidad de la población que atienden, siendo flexibles en su estructura. Es imprescindible la valoración periódica de la calidad asistencial ofrecida, así como la valoración en la rentabilidad de los estudios complementarios a realizar.

Introduction and aims

In January 2012 there were over 5 million foreigners resident in Spain, 15.8% of whom were under 16.[1] Like their parents, immigrant children and those born into families who have arrived recently are at greater risk of suffering from imported diseases unfamiliar to healthcare staff, with certain exceptions such as tuberculosis that are also very prevalent in Spain. In addition, the large number of international adoptions, as well as the increase in travel to low-income countries, are conducive to the presence of these diseases in Spain.[2,3] They are diseases contracted in another country and diagnosed in the host country, where they are either absent or of low prevalence, but they can entail high morbidity and mortality. Although some of them will not be transmitted in the same way as in the country of origin, because of differences in climatic and vectorial conditions, others may represent a potential risk to population health.[4–6]

There are various handbooks devoted to the care of immigrant paediatric patients, and protocols for diagnosis, treatment, and screening in cases of risk of vertical transmission or after trips to high-risk countries.[7–12] Use of protocols, teamwork, and continuing education, as well as specialised training for resident physicians should make it possible to detect and treat imported infections promptly and also to optimise resources devoted to the care of these patients.

In response to the increase in consultations on imported diseases in our unit, a specialised clinic was created in 2009 to provide comprehensive treatment for problems affecting immigrant children or children of immigrants with risk factors and internationally adopted children, as well as those arising from travel to high-risk areas. Since it began we have worked on formulating diagnostic and therapeutic guidelines, set out in various consensus protocols.

This article analyses the first years of operation of our clinic, examining the characteristics of the patients treated and their diseases, and also the advantages of a centralised service in terms of quality of care and teaching.

Patients and methods

We conducted a retrospective study analysing the first three years (January 2009 to December 2011) of operation of the Imported Infectious Diseases Clinic in our unit.

Firstly, we analysed the knowledge generated since its establishment, by evaluating newly formulated protocols and clinical practice guidelines and group work with specialists in other areas and with learned societies, as well as the dissemination of that knowledge through meetings, publications and online communication.

Secondly, we analysed the clinical care delivered in terms of its quality and characteristics. The quality of care provided was assessed in respect of its accessibility. For this purpose we evaluated the delay in initial assessment, defined as the time that elapses from referral to visit, as well as the possibility of consultation by telephone. The study describes patient characteristics, reason for and source of referral, and the disease detected. A descriptive analysis was performed by reviewing the medical histories of patients of paediatric age (<18) seen during the study

Table 1 Examinations included in the protocol, by disease to be ruled out.

Disease group	Examinations to be performed
Infectious disease examination	1. Baseline examination, to be performed for all patients • Baseline serology: anti-hepatitis A virus (HAV) IgG Ab; hepatitis B virus (HBV) markers (HBsAg, HBsAb-IgG, HbcAb-IgG); anti-hepatitis C virus (HCV) IgG Ab; total anti-*Treponema pallidum* Ab and total human immunodeficiency virus (HIV) Ab + Ag p24 • Tuberculosis screening: tuberculin test ± determination of interferon-γ release assays (IGRAs) in the event of history of Bacillus Calmette-Guérin (BCG) vaccination • Parasite examination on fresh stool and using concentration techniques (3 samples) 2. Specific testing according to region of origin • Detection of anti-*Typanozoma cruzi* IgG Ab (2 serological techniques in parallel following WHO diagnostic criteria: native Ag EIA and recombinant Ag EIA) in patients from Latin America, except the Caribbean Islands • Detection of anti-human T-lymphotropic virus 1-2 (HTLV1-2) IgG Ab in patients from Latin America, Africa, Japan and Australia • Detection of anti-*Schistosoma mansoni* IgG Ab in patients from Sub-Saharan Africa or Caribbean countries • Polymerase chain reaction (PCR) of *Plasmodium* spp. and, if positive, for each species separately, for screening of submicroscopic malaria in asymptomatic patients from the Sub-Saharan region of Africa, Central America and Southeast Asia
Eosinophilia examination	Additional tests for patients with eosinophilia[a] in the initial screening. The following are requested: • Parasite examination: stool, urine, serological tests according to protocol[14] • Referral to the allergology service if considered necessary

[a] Eosinophilia: more than 500 eosinophils/μl, in peripheral blood. It is classified as mild (500–1499 eosinophils/μl), moderate (1500–4999 eosinophils/μl) or severe (>5000 eosinophils/μl).

period. We excluded those evaluated in the emergency department or hospitalization, which gave rise to 147 referrals, but did not require subsequent follow-up. In view of the diversity of the patients, and in order to analyse them better, they were grouped into three categories, according to the reason for their assessment.

Group 1 consisted of asymptomatic patients referred for imported disease screening, including adopted and immigrant children attending with their families. Their demographic and clinical characteristics were described: age, sex, anthropometrics (according to Carrascosa's growth curves[13]), region of origin as defined by the WHO,[14] time from arrival in our country to first visit, and referring specialist. We also evaluated the degree of adherence to our protocols in the area of infectious disease, defined as the number of performed examinations compared to the number of examinations that should have been requested according to the risk group, by disease and region of origin. Table 1 shows the examinations performed.

Group 2 included patients who sought services for symptoms of some kind after travel to a tropical or subtropical region. We analysed their demographic and clinical data: age, sex, country visited, type of journey, defined as Visiting Friends and Relatives (VFR: travel whose primary purpose is to visit friends and relatives, where there is a gradient of epidemiological risk between normal place of residence and destination)[15] or non-VFR, whether the patient was assessed or not in a specialised medical unit before travelling, symptoms, and diagnoses performed.

Group 3 contained patients at risk of vertical transmission of imported diseases: patients whose mothers were diagnosed with Chagas disease (ChD), human T-lymphotropic virus (HTLV) or malaria during pregnancy. We analysed their demographic data (age and sex) and maternal data (region of origin) as well as complementary examinations required according to the protocol (Table 2) and diagnoses performed.[16–18] We excluded patients assessed for being at risk of other diseases, such as hepatitis B and C viruses, human immunodeficiency virus and other infections by toxoplasma, rubella, cytomegalovirus, and herpes (TORCH), since these are not classified as imported infections due to their prevalence among native patients.

The statistical study was carried out using the *Statistical Package for the Social Sciences* (v. 20) (SPSS, Chicago, IL, USA). We used the chi-squared test to compare qualitative variables, and set the statistical significance level at $p < 0.05$. This study was approved by the clinical research ethics committee.

Results

With regard to knowledge generated, six diagnostic and therapeutic protocols, available on the unit's website

Table 2 Testing to be performed by protocol in patients at risk of vertical transmission, by disease.

Disease to be ruled out	Examinations to be performed
Chagas disease	1. Patient under the age of 9 months • At birth: microhematocrit test and *T. cruzi* PCR • From age 9 months: serological tests for *T. cruzi* 2. Patient over the age of 9 months • Serological tests for *T. cruzi*
HTLV-I/II infection	1. At birth • HTLV PCR (valid only in cases of maternal HTLV-I infection) 2. Patient over the age of 9 months • Serological tests for HTLV-I/II. If they remain positive, repeat at 12-18 months for definitive diagnosis
Malaria	1. At birth • *Plasmodium* spp. PCR and, if positive, *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* PCR

(www.upiip.com), were formulated.[16–21] In addition, we worked jointly with various learned societies and produced five publications.[22–26] As for the quality of care in terms of accessibility, no delay was observed in access to a first visit. Furthermore, over 85 telephone consultations were made per year, mainly to obtain information about results, minimising impact on the day-to-day lives of families by reducing hospital visits.

316 patients were seen (52.5% boys, 47.5% girls), of whom 191 (60%) belonged to Group 1, 57 (18%) to Group 2 and 68 (22%) to Group 3. A total of 921 visits took place, 661 in person (71.8%) and 260 consultations by telephone (28.2%), giving an overall ratio of 2.9 visits per patient.

Group 1: screening of immigrant patients

This included 191 patients, 29 (15%) adoptees and 162 (85%) immigrants, aged between 3 months and 17 years (median age 10, interquartile range 5 to 12). 59% were male. 70% were referred by their paediatrician for assessment. Of the 29 children from international adoptions, 44.9% came from Eastern Europe and 75.8% of these received their first assessment within six months of their arrival (51.7% within a month). The remaining 162 patients originated mainly from Latin America (67.3%) and paid their first visit longer after their arrival (29.6% within their first six months in Spain). A statistically significant difference was observed on comparing the proportions of adopted versus immigrant children assessed during the first six months after their arrival (75.8% versus 29.6%; $p < 0.001$).

After evaluating the anthropometric data we observed that 9.9% of the patients showed height and weight retardation (height and weight <3rd percentile), 2.1% low weight (<3rd percentile) and 2.1% low height (<3rd percentile). No statistically significant differences were observed between adopted and immigrant children with respect to anthropometric data.

Table 3 shows the degree of compliance with the consensus protocol for the examinations carried out on at-risk patients related to screening of infectious diseases, and the diagnoses performed.

During the follow-up period, 34 (17.8%) patients presented with eosinophilia, with values between 600 and 5300 eosinophils/μl. Of these, 27 had mild eosinophilia, 6 moderate and 1 severe. In 22 of these 34 patients (64.7%) a parasitic infection was diagnosed and in 8 of them mixed parasitic infections were observed. Nine patients were diagnosed with protozoan infections by copro-parasitological examination: *Giardia lamblia* (8) and *Dientamoeba fragilis* (4). In the remaining 13 cases, helminth infections were diagnosed by copro-parasitological, urine-parasitological and/or serological examination: *Schistosoma mansoni* (1) and *Schistosoma haematobium* (3), *Strongyloides stercoralis* (4), *Toxocara canis* (3), *Trichuris trichiura* (2) and *Enterobius vermicularis* (1). In addition to the parasitological examination, all these patients were screened for other non-infectious entities, as well as being given an allergy assessment. Higher eosinophil counts were observed in patients with helminth infections (800–5300 eosonophils/μl, median 1400) compared with those infected with protozoa (600–1400 eosinophils/μl, median 851), as eosinophilia rarely tends to occur in the latter, and the differences between the two aetiologies were statistically significant ($p < 0.001$).

Group 2: consultation after travelling to a tropical or sub-tropical area

This group comprised 57 patients, aged between 5 months and 15 years (median age 4, interquartile range 2–10). 43.8% were male. 45.6% travelled to countries in Latin America, 22.8% to Sub-Saharan Africa, 19.3% to the Indian subcontinent and Southeast Asia, 8.8% to countries of the Mediterranean basin and 3.5% to Eastern Europe. The majority (94.7%) belonged to the VFR group and 18.5% consulted a specialised centre before their journey.

The most common reason for the consultation was gastrointestinal symptoms (52.6%), followed by fever (43.8%). The relevant complementary examinations were performed

Table 3 Group 1: results for adherence to protocol and diagnoses performed.

	Examinations performed (% compared with total at risk)	Diagnoses
Infectious disease	1 Baseline examination • Serological examination: 170/191 (89) • Tuberculosis screening ◯ Tuberculin test: 86/191 (45) ◯ IGRA determination: 32 of 86 with prior tuberculin test (37.2) because of history of BCG vaccination • Parasites in stool: 139/191 (72.7)	• Active hepatitis B ($n = 1$) • Hepatitis C ($n = 2$) • HIV ($n = 2$) • Tuberculosis ◯ Latent tuberculosis infection ($n = 6$) ◯ Pulmonary tuberculosis ($n = 3$) • Intestinal parasitosis ($n = 36$ patients, mixed parasitosis in 8 cases) ◯ 31 infections caused by protozoa: *G. lamblia* (17), *D. fragilis* (14) ◯ 12 infections caused by helminths: *S. stercoralis* (5), *T. trichiura* (3), *H. nana* (2), *E. vermicularis* (2)
	2 Specific examination according to region of origin • *T. cruzi* serology: 100 of 109 (91.7) • HTLV-I/II serology: 20 of 139 (14.3%) • *S. mansoni* serology: 40 of 40 (100) • *Plasmodium* spp. PCR: 24 of 80 (30)	• Chagas disease ($n = 1$) • Asymptomatic malaria ($n = 1$) • *S. masoni* infection ($n = 2$)

according to the symptoms, travel region, and suspected diagnosis. Among the patients with gastrointestinal symptoms the aetiology was found in 27% of the cases: 17% secondary to parasitosis: *D. fragilis* (3), *E. vermicularis* (1), *Cryptosporidium* spp. (1), *S. mansoni* (2), and 10% of bacterial aetiology: *Campylobacter jejuni* (2) and *Shigella sonnei* (1).

Of the patients with febrile symptoms 3 cases of dengue were diagnosed, 2 of malaria caused by *Plasmodium falciparum*, 2 of typhoid fever, 1 of hepatitis A and 1 of visceral leishmaniasis.

Group 3: screening of patients at risk of vertically transmitted imported infectious diseases

This group included 68 patients at risk of vertical transmission of one of the three diseases mentioned (ChD, HTLV or malaria) by maternal infection.

Of the 68 patients, 62 had mothers with ChD, 68% of whom were from Bolivia. 43.5% were male, and they were aged between 0 and 9 (median age 0.6 years, interquartile range 0–3). The complementary examinations described in Table 2 were requested and complete adherence to the protocol was achieved in 91% of the cases, due to five patients being lost to follow-up. Three cases of congenital Chagas disease were diagnosed.

Examination and follow-up were performed for a newborn child of a mother of Ecuadorian origin with HTLV-II infection diagnosed during pregnancy. Breastfeeding was discontinued and follow-up was carried out up to the age of 9 months, with the patient remaining HTLV-II-negative.

During the period studied 5 pregnant women presented with malaria caused by *P. falciparum* (3 from Equatorial Guinea and 2 from Nigeria). PCR for *Plasmodium* spp. was performed on all their children and was negative in all patients.

Following analysis of the patients and assessment of the actions carried out we observed an acceptable level of adherence to the consensus protocols (77.1% overall). It was lower in the screening of immigrant patients group (63.2%), mainly in the screening of tuberculosis, asymptomatic malaria and HTLV.

In general terms we observed that a total of 102 imported infectious diseases were diagnosed, 73 of which occurred in 56 asymptomatic patients in group 1 (29.3% of the total number of patients screened and 75% of the total number of imported diseases detected). 11 viral infections were diagnosed (hepatotropic viruses, dengue and HIV), 6 bacterial (*S. typhi*, *C. jejuni*, *S. sonnei*), 10 by *Mycobacterium tuberculosis* (4 with disease and 6 with latent tuberculosis infection) and 75 parasitic, including 4 cases of ChD, 3 caused by *P. falciparum* and 1 of leishmaniasis.

Discussion

This study analyses the first years of operation of a hospital paediatric unit devoted to the care of imported infectious diseases, examining the patients' characteristics, the advantages of centralised care and the contributions of the unit. It is, moreover, the first published study of this kind that analyses a substantial number of patients.

Protocols were formulated by updating existing guidelines. Outpatient care was centralised and diagnostic and therapeutic follow-up was carried out in conformity with the developed protocols. The quality of care, assessed in terms of accessibility of first contact with the specialist, could be described as very good, given the possibility of immediate access by telephone and absence of delay for the first visit. It was impossible, for logistical reasons, to carry out a patient and/or family satisfaction survey, even though this is key data for evaluating quality of care.

Even though the patients involved in this study were very heterogeneous, classifying them into the three groups mentioned enabled us to carry out a clear and detailed analysis of the current state of the clinic. In contrast to other studies, an assessment of adherence to agreed protocols was conducted, beyond the clinical and demographic description of the patients.

We observed a high frequency of infectious diseases in the group of asymptomatic patients. The screening programmes enabled us to diagnose diseases with few clinical manifestations that could pose a risk to both individual and public health, without incurring high healthcare costs. Overall we observed acceptable adherence to the protocol, although one must be critical of some results. The percentage of patients screened for tuberculosis was strikingly low (45%). Despite following WHO screening recommendations we can see that coverage with the tuberculin test in our study remains low.[27,28] 10.5% of the 86 patients studied presented with *M. tuberculosis* infection. Many patients were probably screened in their health centres, and therefore a new determination at the time of our assessment was not considered necessary, but this information is difficult to obtain, since part of the study was carried out before the introduction of shared electronic medical histories. Even so, we wish to stress the importance of proper tuberculosis screening for appropriate management both of patients and of epidemiological control in our society.

Regarding the initial study of intestinal parasitoses, and the directed search for them in the eosinophilia study, we observed a high percentage of parasitic infections in asymptomatic patients.

As has been commented, targeted testing is recommended for the screening of some infectious diseases, such as ChD, HTLV or *Plasmodium* spp., according to the place of origin. For patients assessed and at risk of ChD we observed appropriate testing by serological tests, with adherence to the protocol of over 90%. With regard to HTLV infection, a review of the literature, excluding screening of vertical transmission, reveals no conclusive data for screening in asymptomatic children from high-risk areas.[29,30] In our study, serological tests were requested when confronted with HTLV in 14.3% of the patients at risk, without any infected patients being observed, and it has therefore been eliminated from the routine examination of immigrant patients. As for infection by *Plasmodium* spp., several cases of asymptomatic or submicroscopic malaria have been described, mainly by *P. falciparum* in patients from Sub-Saharan Africa.[31–34] Although there is no consensus for screening in asymptomatic patients, it seems clear that they should be tested using PCR techniques, especially in at-risk groups such as pregnant women, children and HIV patients from endemic areas.[32,34] In our study, 30% of the patients at risk were examined for submicroscopic malaria, with one positive for *P. falciparum*, which represents 4% of those tested, similar to the prevalence found by Matisz et al.[33] This is a point of improvement and may be due to the excellent state of the patients at the time of the consultation.

Our analysis of patients seen after travel to high-risk areas showed appropriate follow-up of these patients. The main symptoms observed, consistent with the literature, were gastrointestinal symptoms and fever.[35–37] Although the high risk of exposure to potentially serious diseases is well known, the rate of medical consultation before travelling was strikingly low, as is also the case in other studies.[37] We think it is important to emphasise the desirability, for families planning such journeys, of being assessed at a specialised international vaccination centre, as a way of improving prophylaxis, vaccinations and other general measures.

In the vertical transmission risk group we observed adherence to the protocols of close to 100%. The study published by our group in 2012 describes the impact of the implementation of ChD screening on at-risk pregnant women.[24] Our study included patients at risk of vertical transmission and also patients outside the neonatal period, and this enabled us to diagnose and treat three patients infected by *T. cruzi*. As is the case with ChD, studies have been published on the screening of pregnant women at risk of HTLV, although this type of screening is not established as a routine procedure in pregnancy.[17,29,30]. The same cannot be said of the risk of congenital malaria, where there are little published data on the control and follow-up of these newborns. We therefore consider that consensus practice guidelines are needed for better management of these patients.[9,18]

The aim of this study, as well as analysing our patients and the actions taken, is to make healthcare staff aware of the importance of these diseases. We believe that further studies along these lines are needed in order to be able to define which examinations for assessing these diseases are really necessary and cost-efficient.

The limitations of our study are its retrospective character and also the lack of indicators of population coverage in the screening of these diseases. Nevertheless, it offers a detailed description of the current state of the clinic, in terms both of clinical and demographic data and of quality of care and teaching.

The changes that are taking place in patterns of migration and socio-economic conditions will force us to adapt units of this kind to the new realities.

Conflicts of interest

The authors have no conflicts of interest to declare.

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