Background and Purpose: Malaria had been eradicated in Taiwan since 1965, but there are currently 30 to 50 imported cases annually. The management of imported malaria continues to be challenging due to evolving drug resistance of *Plasmodium* parasites.

Methods: We retrospectively analyzed the clinical presentations, treatment, and outcomes of all 16 adult patients (17 episodes) with imported malaria diagnosed during 1999-2005. The clinical and laboratory features were obtained from the medical records.

Results: Malaria was acquired in sub-Saharan Africa in 6 cases and Southeast Asia in 11 cases. The initial presentations were nonspecific, including fever (17/17 cases), headache (11/17), nausea, vomiting or diarrhea (10/17), cough (3/17), thrombocytopenia (15/17), mild hyperbilirubinemia (13/17), leukopenia (6/17) and anemia (4/17). Careful travel history led to the correct diagnosis in 16 of 17 cases. All 17 cases survived without any recrudescence. Four cases presented with hyperparasitaemia (>5%). Two patients were admitted to an intensive care unit for complicated malaria, and both were cured by artesunate plus mefloquine. Some suboptimal practices, such as non-standard therapeutic regimen and lack of daily parasitemia counting were noted.

Conclusions: A differential diagnosis of malaria should be made in all patients who have fever after travel to any endemic area. To further improve the management of imported malaria, timely consultation of an experienced infectious disease specialist is necessary.

Key words: Artesunate; Combination drug therapy; Malaria; *Plasmodium falciparum*; *Plasmodium vivax*

Introduction

Malaria is an important infectious disease worldwide. According to recent data from the World Health Organization (WHO), there are more than one million deaths and up to 500 million clinical malaria cases each year, mainly in Africa and Southeast Asia [1]. Although malaria has been eradicated in Taiwan since 1965 [2], there are approximately 30 to 50 imported cases annually [3]. The management of imported malaria continues to be challenging due to evolving drug resistance of *Plasmodium* parasites. Chloroquine has not been effective for the treatment of *Plasmodium falciparum* malaria since the early 1990s. The efficacy of sulfadoxine-pyrimethamine (SP) also rapidly declined in the mid-1990s [4]. Quinine has become the first-line therapy for imported malaria in Taiwan since 1992. To minimize recrudescence, a consolidation course of mefloquine has been recommended after completion of the quinine therapy [5]. However, multiresistant *P. falciparum* strains non-susceptible to chloroquine, SP, mefloquine and quinine, have emerged in the Thai-Cambodian border area and elsewhere [6,7]. As a result, imported malaria cases in Taiwan have become more and more difficult to treat in the 21st century. In the meantime, newer and less toxic regimens, such as artemisinin-based combination regimen (ACT), emerged as an alternative to quinine therapy.
To evaluate the current situation and identify problems in the management of imported malaria in Taiwan, we retrospectively analyzed the clinical presentations, treatment, and outcomes of 16 consecutive patients with 17 episodes of malaria treated at the National Taiwan University Hospital (NTUH) from 1999 through 2005.

Methods

All malaria patients treated at NTUH from 1999 through 2005 were included in this study. The diagnosis of malaria and the identification of species were based on microscopic examination of thin blood smears. The results were further confirmed by parasitologists from the Laboratory Research and Development Center, Centers for Disease Control, Department of Health, Executive Yuan, Taiwan. Hyperparasitemia was defined as more than 5% of infected peripheral red blood cells. Severe falciparum malaria is defined as the occurrence of any one of the following conditions at presentation or during hospitalization: cerebral malaria, generalized convulsions, metabolic acidosis with respiratory distress, acute renal failure, acute pulmonary edema, adult respiratory distress syndrome, circulatory collapse, or shock [8]. The clinical and laboratory features of each case, from presentations to outcomes, were obtained from the medical records.

Results

Demographic and geographic features

Sixteen adult patients with malaria were treated at NTUH from 1999 through 2005. One patient had two separate episodes of Plasmodium vivax infection. The interval between these two episodes was 4 months and the two episodes were acquired in two different countries. He received complete chloroquine plus primaquine therapy in the first vivax malaria episode, so reinfection rather than relapse was likely. Thus, there were in total 17 cases of malaria during the past 6 years.

Of these 16 patients, 8 were foreign nationals and 8 were Taiwanese citizens. Most (10/16) of these patients were men, with a male-to-female ratio of 10:6, and a median age of 36 years (range, 20-77 years). P. falciparum was identified as the causative species in 8 cases (including 2 cases of mixed infections with P. falciparum and P. vivax), P. vivax in 9 cases, and Plasmodium malariae in 2 cases. Malaria was acquired in sub-Saharan Africa in 6 cases (5 P. falciparum, 1 P. malariae), and Southeast Asia in 11 cases (2 mixed infection, 7 P. vivax, 1 P. falciparum and 1 P. malariae). All P. vivax infections were acquired in Southeast Asia. Three P. falciparum cases, 3 P. vivax cases (including one of mixed infection) and both P. malariae cases had previous malaria infection histories. Chloroquine was the chemoprophylactic agent. All 8 Taiwanese patients did not have good compliance with the chemoprophylactic drug therapy when traveling to the endemic areas. Seven patients had past histories of malaria infection; 3 were Taiwanese and 4 were foreign nationals.

Clinical and laboratory presentations

Fever was the initial manifestation in all cases, and 11 cases had headache. Three cases developed hyperpyrexia with a body temperature above 40°C. Seven of the 17 cases had the characteristic fever patterns — several chill-fever episodes within a day (P. falciparum infection) or tertian fever (P. vivax or P. malariae infection). Myalgia or arthralgia was more common in patients infected with P. vivax than in those infected with P. falciparum. One patient with cerebral malaria (mixed infection) presented with binocular blindness and altered consciousness in the emergency room (ER). Symptoms mimicking gastroenteritis and upper respiratory tract infection occurred in 10 and 3 cases, respectively.

All 17 cases were admitted to this hospital via the ER. The most common initial laboratory abnormalities were thrombocytopenia (platelet count <100 × 10^9/L) and hyperbilirubinemia (serum bilirubin level >1.2 mg/dL) [Table 1]. Thrombocytopenia can be severe, ranging from 14 × 10^9/L to 83 × 10^9/L (median, 60 × 10^9/L) in patients with falciparum malaria, and ranging from 4 × 10^9/L to 92 × 10^9/L (median, 66 × 10^9/L) in those with tertian malaria. Initial leukopenia (<4.0 × 10^9/L) was found in both patients infected with P. malariae, but was not common in patients infected with P. falciparum or P. vivax, with 1 (12.5%) and 3 cases (38%), respectively. Only 4 cases had anemia (hemoglobin <11 g/dL) in the ER, but another six cases developed anemia during hospitalization. Hyperbilirubinemia was usually mild, with a median serum bilirubin of 2.3 mg/dL in cases with falciparum malaria, and 1.85 mg/dL in cases with tertian malaria. Serum glucose level was not evaluated in all patients, but none had hypoglycemic symptom complaints. There was no bacterial coinfection in any patient. With careful history review, the diagnosis of malaria was made on the day visiting the hospital by an infectious disease
specialist in 16 cases. The travel history was neglected in one patient until the characteristic tertian fever occurred during hospitalization. The interval between admission and diagnosis in this patient was 3 days.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one who had cerebral malaria with mixed infection.

Therapy for malaria and drug toxicity
The regimens of antimalarial therapy are summarized in Table 2.

Severe malaria
There were 4 cases of severe malaria. Two cases received artemesunate plus mefloquine; one quinine plus mefloquine plus doxycycline, and one received chloroquine plus mefloquine (Table 2). One patient with cerebral malaria was treated with artemesunate plus mefloquine for *falciparum* malaria and artemesunate plus primaquine for *vivax* malaria. This patient suffered from artemesunate-related reticulocytopenia and mefloquine-related frequent ventricular premature contractions. This patient also had severe anemia (hemoglobin of 3.5 g/dL), which developed after 4 days of primaquine, but her glucose-6-phosphate dehydrogenase (G6PD) level was normal (19.41 U/g). These complications resolved spontaneously without regimen adjustment. The other patient treated with artemesunate initially received quinine therapy, and then artemesunate plus mefloquine. This patient developed tinnitus, blurred vision, and non-cardiogenic shock after one day of quinine therapy. There was no abnormality in electrocardiography and the above complaints disappeared after quinine was discontinued. However, this patient received transient ventilator support and hemodialysis. The patient who received quinine plus mefloquine plus doxycycline therapy also had tinnitus after one day of quinine therapy, and no regimen adjustment was done. The patient returning from Nigeria, an endemic area with chloroquine-resistant malaria, received chloroquine plus mefloquine therapy. Although relative hypotension occurred after treatment in this patient, the regimen was not changed.

The duration from starting anti-*falciparum* malaria treatment to defervescence was 4, 6, 12, and 17 days,
respectively; and to clearance of parasitemia was 3, 4, 5, and 7 days, respectively. The two cases with intensive care unit support had a prolonged duration from starting antimalarials to defervescence, 12 and 17 days, respectively. All 4 patients survived and no recrudescence was noted.

### Uncomplicated malaria

In the *falciparum* malaria group, 2 patients received quinine plus mefloquine, 1 patient received quinine plus doxycycline, and 1 patient who had mixed infection with *P. vivax* received artesunate plus mefloquine therapy (Table 2). One other patient received chloroquine plus primaquine for *vivax* malaria. No drug-related toxicity was observed.

The duration from starting anti-*falciparum* malaria treatment to defervescence was 0, 2, 3, and 4 days, respectively. The duration to clearance of the parasitemia was unknown for 1 patient because blood smear was not monitored daily. This patient had defervescence on the fourth day after artesunate plus mefloquine therapy and another blood smear resulted in a negative finding on the twelfth day after antimalarials. The duration to clearance of parasitemia was 2, 3, and 3 days, respectively. Under the above treatment, all patients survived and no recrudescence was noted.

Nine cases were infected with *P. vivax*, and 2 were co-infected with *P. falciparum*. Seven cases received standard chloroquine plus primaquine therapy for *P. vivax* infection. Two patients with *P. vivax* infection received a combination regimen with artesunate plus mefloquine and quinine plus doxycycline. One patient in the combination therapy group had transient prolonged corrected QT interval (QTc) in the electrocardiography after quinine therapy, but no regimen adjustment was performed. Chloroquine plus primaquine was used in 1 *P. malariae*-infected patient and quinine plus mefloquine was used in the other one (Table 2).

The duration from starting antimalarials to defervescence ranged from 1 to 4 days and the time to clearance of parasitemia ranged from 2 to 7 days. The blood smear of the patient who had 2 episodes of *vivax* malaria was not monitored again after malaria was diagnosed. This patient had defervescence after 1 and 3 days of antimalarials in these episodes.

### Discussion

Responding to evolving drug resistance, the WHO revised the antimalarial therapy recommendation in 2006. ACT currently is the first-line therapy for severe malaria. Two cases of severe malaria were treated...
with ACT as the first-line therapy at NTUH. Both patients, including the one who had cerebral malaria [9], recovered smoothly. Because of three previously reported cases of intravenous quinine-related life-threatening cardiotoxicity, intravenous quinine was no longer used at NTUH after 1998 [10].

In Taiwan, oral chloroquine (chloroquine phosphate 2500 mg given over 3 days) plus primaquine (15 mg/day for 14 days) was given as the initial therapy for falciparum malaria from 1958 until the early 1990s [11]. Quinine (10 mg/kg three times daily for 3-7 days) was used as the first-line therapy for falciparum malaria since the early 1990s [11]. To ensure complete cure without recrudescence, a second drug (SP during 1992-1994, and mefloquine after 1994) which is effective against P. falciparum was given as consolidation therapy after the completion of quinine or artesunate therapy [10]. Tetracycline (250 mg every 6 h for 3-7 days) or doxycycline (100 mg every 12 h for 7 days) was added in cases acquired in Southeast Asia [12]. Mefloquine is still effective in Africa [13], and might have resistance in Southeast Asia [6,7]. Quinine plus mefloquine was given to patients who came from sub-Saharan Africa and quinine plus doxycycline was given to those who came from Southeast Asia in this study. Currently, artesunate (4 mg/kg/day for 3 days) plus mefloquine (1500 mg over 24 h for a body weight >60 kg, 1250 mg for a body weight <60 kg) is listed as the first-line therapy for falciparum malaria in Taiwan. Quinine plus doxycycline is the alternative anti-falciparum agent if artesunate is not available or contraindicated [14].

The toxicity of quinine is associated with cinchonism, which can be mild, with tinnitus and blurred vision, to severe, with vomiting, diarrhea, and vertigo. Quinine commonly causes hyperinsulinemic hypoglycemia. The adverse effects of quinine that physicians are mostly concerned of are the increase in QTc interval and QRS widening [15]. Two of 6 patients (33%) treated with quinine and 1 patient who had severe malaria had cinchonism complications. The toxicity of artesminin derivatives is significantly less than quinine and the drug adherence is better, although there were occasional reports of reticulocytopenia, mild gastrointestinal disturbance, dizziness, and tinnitus after therapy with artesminin derivatives [15]. In addition to a lower risk of severe adverse effects, artesminin derivatives also appear to have a better efficacy against Plasmodium than quinine [16,17]. Dondorp et al showed an absolute mortality reduction of 34.7% in the artesunate group compared to the quinine group [17]. In 2006, WHO recommended artesunate as the first-line therapy for falciparum malaria and quinine as the alternative agent [13]. Unfortunately, artesunate is not licensed in Taiwan, and the major concern is that artesunate is not produced following good manufacturing practice [17].

In addition to drug therapy, several issues were highlighted in this study. First, the nonspecific initial presentations increase the difficulty of a diagnosis of malaria. Second, there was a lack of experience of junior physicians in malaria management. In this study, most patients had nonspecific initial presentations, the majority with fever, headache, thrombocytopenia, and hyperbilirubinemia. Some patients had additional diarrhea, myalgia or arthralgia, and cough, which may confound the diagnosis. Absence of anemia, hepatomegaly or splenomegaly was common. If the travel history is not carefully taken, the diagnosis and treatment of imported malaria can be delayed [8,10,18]. In five patients, although the travel history suggested malaria infections, malaria was still not impressed by junior emergency physicians. The interval from symptoms onset to visiting our emergency department was 1 to 10 days. Fever of unknown origin, rickettsia disease, Q fever or intra-abdominal infection were suspected. Four cases were diagnosed and treated immediately after an infectious disease specialist consultation.

Five patients received a “non-standard” antimalarial regimen. One Taiwanese patient with severe falciparum malaria acquired in Nigeria received chloroquine therapy initially. Since P. falciparum is usually resistant to chloroquine in West Africa, this drug is not an appropriate initial choice. The mefloquine resistance in Africa is currently being further reviewed, and use of chloroquine plus mefloquine may risk treatment failure [13]. Two patients received concurrent artesunate and quinine for P. vivax acquired in Indonesia. This regimen was an overtreatment. Although there were sporadic case reports of chloroquine-resistant vivax malaria [19-23], chloroquine is still generally effective for vivax malaria acquired in Indonesia [13]. Use of concurrent artesunate and quinine in this scenario will cause an unjustified increase in the risk of serious arrhythmia [24]. For P. malariae infection, single-agent treatment with chloroquine should be enough [13,25,26]. However, one patient who had P. malariae infection received chloroquine and additional primaquine therapy, and the other patient received quinine followed by mefloquine therapy. In both patients, the non-standard regimens are associated with an increased risk of adverse drug reactions, such as quinine-related life-threatening arrhythmia, primaquine-related hemolysis.
Imported malaria

Another suboptimal practice was the lack of daily parasitemia evaluation in three cases. Because there is no practical susceptibility testing for malaria parasites, parasitemia evaluation is the only method for detection of drug resistance [8]. Without daily parasitemia monitoring, it will be difficult to differentiate serious adverse drug effects, such as quinine-related shock and lung edema and primaquine-related hemolysis, from uncontrolled drug-resistant malaria. Different approaches are required for the management of these two conditions. Therefore, it is imperative to monitor parasitemia until the clearance of the malaria parasite from blood. In addition to parasitemia evaluation, another underused test is measurement of serum levels of G6PD (only 4 of 10 cases with primaquine therapy had their G6PD level tested). In individuals with G6PD deficiency, primaquine therapy can cause serious hemolysis. Ideally, plasma G6PD levels should be monitored before the start of primaquine for patients with vivax malaria [15].

In conclusion, the initial nonspecific presentations of imported malaria increased the difficulty of diagnosis of malaria. A differential diagnosis of malaria should be considered for all febrile patients returning from endemic areas. Some suboptimal practices, such as non-standard therapeutic regimen and lack of daily parasitemia evaluation were noted in this study. To further improve the management of imported malaria, timely consultation with an experienced infectious disease specialist is necessary.

References
11. Centers for Disease Control. Malaria eradication in Taiwan. 2nd ed. Taipei, Taiwan: Centers for Disease Control; 2005.
20. Soto J, Toledo J, Gutierrez P, Luzz M, Llinas N, Cedeno N,


