# Histoplasmosis: Long term remission following treatment with low dose amphotericin-B

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## SUMMARY

Three patients with oro-pharyngeal histoplasmosis and systemic involvement were treated with a minimal total amount of Amphotericin-B administered intermittently in low dosage because of serious toxic reactions. The drug was given in 10 – 25 mg doses approximately 2 – 3 times a week and total amounts administered varied between 130 mg and 500 mg over 6 to 15 weeks. All patients responded to treatment and healing of lesions was observed several weeks after cessation of therapy. It is suggested that such minimal doses of Amphotericin-B may suffice in treatment of patients with invasive histoplasmosis especially when serious toxic reactions are encountered.

## INTRODUCTION

Amphotericin-B in maximum tolerated doses is generally accepted as appropriate therapy for systemic histoplasmosis. This current practice is not entirely satisfactory because such high doses of Amphotericin-B frequently produces serious toxic reactions and requires prolonged hospitalisation. Information concerning a minimal effective dose must be determined by appropriate observations in man, because data on the pharmocology of Amphotericin-B do not at the present time suffice for defining a rational dosage scheme.

Generally a cumulative dose of at least 3 gms of Amphotericin-B is recommended as minimum treatment for most patients with invasive mycoses such as sytemic histoplasmosis. However referrals to the literature has not clarified the basis for this commonly accepted scheme of therapy.

In this paper we present 3 patients with oropharyngeal histoplasmosis with systemic involvement, all of whom were positively diagnosed on the basis of both histopathology and culture studies and who were treated with a very much lower dosage of Amphotericin-B than recommended. We report long term remissions in these patients and would suggest that the administration of Amphotericin-B be deliberately reviewed in the light of our findings.

## CASE REPORT

*CASE 1* L.Y. was a male Chinese patient aged 54 years from Puchong. He worked as a motor mechanic and had been in this occupation for the last 30 years. He was first seen at the General Hospital, Kuala Lumpur in March 1972 complain-

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ing of weight loss generalised weakness and easy fatigability for a period of about 6 months. He had lost about 35 lbs and weighed 102 lbs when seen. A month before admission he had developed painful oral ulcers and nodules which made it difficult for him to swallow. He had no past medical history of significance.

On examination he appeared ill, his blood pressure was 110/70, and he had several ulcers and nodules within his oral cavity, (Fig 1 and 2).

Investigations revealed haemoglobin 14.2 gm/100 ml, total white count 15,800 (P=784, L=184, B=2%), platelets counts 320,000/cu mm, blood urea 31 mg%, Serum Na 140 meg/L, Potassium 4.0 meg/L, Chlorides 102 meg/L, urinalysis negative for sugar and albumen, no urinary deposits, serum bilirubin 0.8 mg%, serum alkaline phosphatase 28 KA Units, Serum albumen 3.2 gm/100 ml, serum globulin 3.8 gm/100 ml, serum gultanic oxalate transaminase 87 I.U. sputum negative for acid fast organisms, chest and abdominal x-rays negative, plasma cortisol 14 micrograms/100 ml (following Synacthen stimulation-22 micrograms/100 ml). Histoplasmosis was diagnosed both by identification in histopatho - logical sections taken from oral nodules (Fig 3) as well as by culture in sputum and bone marrow.

Treatment with Amphotericin-B was initially started at a dose of 20 mg per 500 mls of 5% Dextrose. However this dosage had to be reduced because of severe neuritic pains the patient developed in his ulna and popliteal nerves which appeared to be dose related. Over a period of 15 weeks a total of 410 mg of Amphotericin-B was infused at approximately 10 mg thrice weekly. This treatment had then to be discontinued because nerve pains became intolerable and a wrist drop developed in his right hand. Concomitant use of steriods was helpful but did not completely relieve the symptoms. At the time of discontinuation of therapy there was some improvement seen in the oral ulcers but these had not completely disappeared. Blood and sputum cultures became negative four weeks after commencement of therapy. He was followed up subsequently and it was observed that these ulcers and nodules progressively disappeared over a period of 6 to 8 months (Fig 4). During this time he reported increased well-being and a return of appetite. His weight increased from 102 lbs over the next year to around 140 lbs. Neuritic pains however continued to occur for several months after healing of oral ulcers. He was last reviewed in May this year at which time he appeared to be well and had no symptoms-24 months after cessation of therapy.

*CASE 2* This was a 53 year old male, Indian hospital assistant A.P., who was referred to our care in May, 1972. He had developed prolonged fever for more than three months and had been treated with a variety of antibiotics without very much relief. He also complained of increasing weakness and loss of weight. About one month earlier he was given a course of Prednisolone which resulted in the fever subsiding but symptoms recurred on stopping the medication. On examination in Kuala Lumpur he was found to be febrile and slightly jaundiced. The liver was enlarged to 4 cm below the costal margin and was slightly tender. The left tonsil was noted to be larger than the right and covered with a whitish exudate. No neck glands were felt. Haemoglobin, full blood counts, urinalysis, blood urea, serum electrolytes, serum creatinine, serum proteins, ECG, chest x-rays were all normal. Sputum was negative for acid-fast organisms. Serum Bilirubin was 1.8 mg%, alkaline phosphatase 28 KA Units and SGPT 120 I.U. Biopsy of the tonsil which was removed showed the presence of Histoplasma Capsulation. Subsequently positive cultures from the tonsil also confirned the diagnosis. Sputum urine and blood did not yield positive cultures. He was treated with Amphotericin-B with few side effects and there was good patient acceptability at 25 mg infusion dose. The drug was given as a slow intravenous infusion in 500 ml of 5% Dextrose at 25 mg thrice weekly and treatment was discontinued after infusion of a total dose of 500 mg or Amphotericin-B over a period of 10 weeks. The patient became afebrile in one week and has been well for the past 18 months.

CASE 3 Mr. N.H., a 61 year old Malay Mining Engineer from Burma came to us early this year. He complained of extreme loss of weight (more than 48 lbs) and felt weak, tired easily and had severe anorexia. He had developed ulcers in the right mandibular sulcus region, over the previous 2 to 3 months and had attributed this to an abrasion from his dentures. He had seen several doctors both in Burma and in Kuala Lumpur and had been given various types of treatment the nature of which was not known. When seen, he weighed 101 lb and appeared very weak and emaciated. His blood pressure was 90/50 and he had mild oedema of his ankles. Investigations revealed abnormal chest x-ray

showing diffuse mottling (compatible with pulmonary histoplasmosis), abnormal liver function test (SGPT 88 I.U. and serum albumin 2.4 gm) and adrenal insufficiency (basal levels of plasmocortisol 6.3 micrograms and after Synecthen stimulation, 6.7 micrograms). Histoplasmosis was confirmed from biopsy of the oral ulcer and culture of sputum urine and blood. He was started on Amphotericin-B at 10 mg dose levels and increased to 25 mg daily but this dose had to be reduced because of runs of ventricular ectopics, transient heart blocks, hypotension and axotaemia. Treatment with Amphotericin-B was continued at approximately 15 mg twice weekly over a period of six weeks during which time 125 mg of the drug was given. Subsequent administrations caused severe rigors and haematuria even though an attempt was made to reduce the dosage. The units of 5% Dextrose used were analysed at 3 different independent laboratories in Kuala Lumpur and Germany and were reported to be both bacteria and pyrogen free. A further 15 mg of the drug were given in 5% Dextrose after a short pause but the patient again developed severe rigors and complained of oppresive chest pains. ECG's taken at this point showed that he had developed an acute myocardial infarction. Amphotericin-B was discontinued on the basis that further infusions appeared to carry a real risk of serious myocardial and renal damage. The patient meanwhile was given tablets of Cortisone Acetate and intermittent injections of "Synecthen retard".

On follow-up he showed increased well-being with a return of appetite. His weight increased from 101 lbs to 120 lbs when last seen about a month ago. Cultures of urine became negative 3 weeks after treatment and continue to be negative. All ulcers showed progressive healing after cessation of therapy. He remains well 5 months after Amphothericin-B was discontinued.

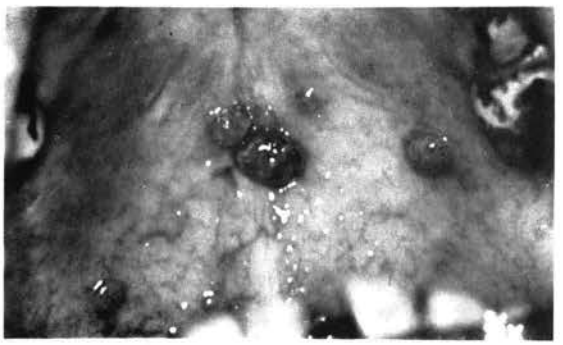
## DISCUSSION

It is generally agreed that spontaneous recovery from invasive histoplasmosis occurs uncommonly (Furcolow M.L. et. al. 1963). However there has been no agreement on the minimum dose of Amphotericin-B required to treat such patients both effectively and safely (Sutliff D.W. 1972). Previous observations that doses below 1 mg/kg/day (Andiole V.T. et. al. 1962) are ineffective are not generally accepted (Drutz D.J. et. al. 1968 and Sutliff D.W. 1972). Thus far determation of daily dosage and duration of treatment appears to be based on the limits of toxicity that the patient can accept and the primary goal has been to stay as close as possible to maximally tolerated doses.

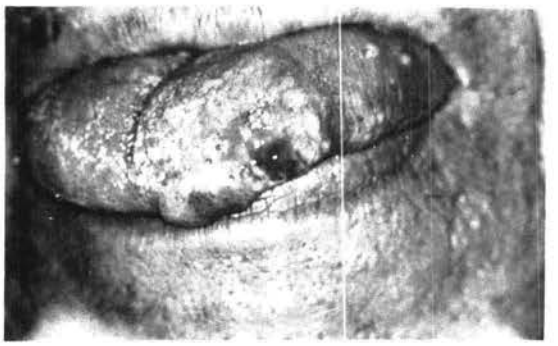
In the case of Amphotericin-B a full understanding of its pharmocology and structure and fate within the body have not been clearly elucidated. Its mechanism of action has been described as a reaction with lipid components of cell walls and lysosomal membrane but quantitative interpretation of these reactions and the degree to which these affect host tissues have not been clearly defined. The question of dosage therefore of Amphotericin-B will continue to rely on clinical experience derived from patient treatment. It is possible that in an indolent infection such as histoplasmosis host-parasite relationships could be altered in favour of defence mechanisms with a minimal dose of the antifungal drug. What the exact mechanism of body defences against low grade infections of this type has not been clear from previous studies.

It has been suggested that a dose of 50 mg of Amphotericin-B given thrice weekly over 17 weeks appeared to control most patients with prodominant chronic pulmonary histoplasmosis (Sutliff D.W. 1972). On this study it was recommended that this type of smaller total dosage with retreatment when necessary appeared to be a logical procedure considering the serious side effects with the use of the drug. Even at these doses it is conceded that toxic effects in patients appear to be significant.

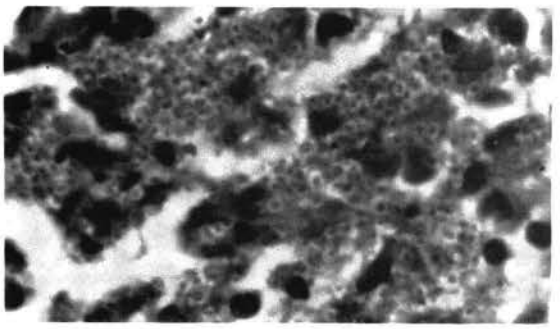
In our series, serious side effects forced us to use much lower doses during each infusion in the treatment of our patients. Further, marked toxicity also prevented administration of a planned cumulative dose which would appear to be optimal by previous recommendations. We have been impressed by the fact that continued patient well-being and resolution of tissue involvement has occured on these doses long after the drug has been discontinued. It would appear that response to treatment would continue after drug administration has ceased. In one of our patients (Case 2) we deliberately used smaller daily doses in spite of greater patient tolerance and observed similar long lasting improvement. In another patient (Case 3) there was laboratory and clinical evidence of adrenal insufficiency and though such patients are regarded as being seriously ill with a high mortality rate (Sarosi, G.A. et. al. 1971), this patient has shown surprisingly good recovery. We do not discount the possibility that retreatment in our patients may be necessary at a



*Shows nodules on the palate.*
*Fig. 1*



*Shows a chronic ulcer on the left margin of tongue.* *Fig. 2*



*Photomicrograph shows Histoplasma Capsulatum in a biopsy taken from the tongue ulcer. (Orig. mag x 120/PAS stain).*
*Fig. 3*

*Shows regression of nodules on the palate, (Compare Fig 1).*
*Fig. 4*

later date. However the desired response coupled with increased patient safety prompts us to recommend lower doses of Amphotericin-B in patients with disseminated histoplasmosis.

Admittedly this series is uncontrolled and too small for firm conclusions regarding Amphotericin-B dosage to be generally applied for treatment of patients with invasive histoplasmosis. However we conclude that these observations do suggest that a much lower cumulative dose of Amphotericin-B administered in lower intermittent doses for patients with the disease may suffice and is worthwhile considering in those who develop serious side effects during therapy.

## ADDENDUM

Since submission of this manuscript for publication two of our patients have had clinical signs of relapse. Although cultures of body fluids have been negative we have proceeded with re-treatment using minimal doses as indicated in this publication.

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