



## The new generation broad-spectrum penicillin

### INDICATIONS AND DOSAGE

Infections of the ear, nose and throat due to streptococci, pneumococci, and penicillin-sensitive staphylococci; infections of the upper respiratory tract due to *H. influenzae*; infections of the genitourinary tract due to *E. coli*, *P. mirabilis*, and *S. faecalis*; infections of the skin and soft tissues due to streptococci, penicillin-sensitive staphylococci and *E. coli*:

### USUAL DOSE:

**ADULTS** 250 mg every 8 hours

**CHILDREN** 25 mg/kg/day in divided doses every 8 hours

In severe infections or infection associated with organisms where sensitivity determinations indicate higher blood levels may be advisable: 500 mg every 8 hours for adults, and 50 mg/kg/day in divided doses every 8 hours for children may be needed. This dosage should not exceed the recommended adult dosage.

Infections of the lower respiratory tract due to streptococci, pneumococci, penicillin-sensitive staphylococci and *H. influenzae*:

### USUAL DOSE:

**ADULTS** 500 mg every 8 hours

**CHILDREN** 50 mg/kg/day in divided doses every 8 hours

This dosage should not exceed the recommended adult dosage.

**Urethritis** due to *N. gonorrhoeae*: 3 g as a single oral dose.

### CONTRAINDICATION

In patients with a history of allergy to the penicillins and cephalosporins.

Product Monograph available on request.

### SUPPLIED

**AMOXIL-250 Capsules**—each contains 250 mg amoxicillin (as the trihydrate)

**AMOXIL-500 Capsules**—each contains 500 mg amoxicillin (as the trihydrate)

**AMOXIL-125 Suspension**—125 mg amoxicillin per 5 ml, in 75 ml & 100 ml bottles

**AMOXIL-250 Suspension**—250 mg amoxicillin per 5 ml, in 75 ml & 100 ml bottles

**AMOXIL Pediatric Drops**—15 ml (50 mg/ml) in dropper bottle

**Ayerst**

Quality has no substitute

AYERST LABORATORIES

Division of Ayerst,  
McKenna & Harrison Limited  
Montreal, Canada

Made in Canada by arrangement  
with BEECHAM, INC.

\*Reg'd

## St. Louis encephalitis in southern Ontario: laboratory studies for arboviruses

L. SPENCE, FRCP[C]; H. ARTSOB, PH D;

L. GRANT, MB, DIP BACT, MPH, FRC PATH; C. TH'NG, B SC

**The first reported outbreak of St. Louis encephalitis in Canada occurred in the summer of 1975 in southern Ontario — in the Windsor-Sarnia-Chatham area, the Niagara region and the city of Toronto. Hemagglutination inhibition and complement fixation testing of serum samples collected during the outbreak confirmed that St. Louis encephalitis virus was the etiologic agent. Furthermore, this virus was isolated from brain tissue of a patient who died. This outbreak was probably an extension of the outbreak that occurred in the United States that summer. It was the first outbreak of arbovirus encephalitis in the province of Ontario.**

**La première épidémie d'encéphalite de St-Louis à être signalée au Canada est survenue durant l'été de 1975 dans le sud de l'Ontario dans la région de Windsor-Sarnia-Chatham, la région de Niagara et la ville de Toronto. Les épreuves d'inhibition de l'hémagglutination et de fixation du complément des échantillons de sérum prélevés durant l'épidémie ont confirmé que le virus de l'encéphalite de St-Louis était l'agent infectieux. De plus, le virus a pu être isolé du cerveau d'un patient qui est décédé. Cette épidémie est probablement une extension de l'épidémie enregistrée aux États-Unis durant le même été. C'était là la première épidémie d'encéphalite à arbovirus signalée en Ontario.**

In the summer of 1975 an outbreak of encephalitis occurred among residents of southern Ontario. Intensive laboratory investigations were carried out during the outbreak. This report is the first of a series dealing with the clinical, epidemiologic and virologic aspects of the outbreak. It describes the arbovirus investigations carried out on specimens submitted from all parts of Ontario during the summer of 1975 to the National Arbovirus Reference Service, a laboratory in Toronto oper-

ating in conjunction with the Laboratory Centre for Disease Control of Health and Welfare Canada.

### Epidemiologic and clinical aspects

The outbreak began at the end of July and continued into October. The most severely affected area was the city of Windsor but patients were encountered in other localities in southern Ontario, including the Niagara peninsula and the city of Toronto.

Patients admitted to hospital had symptoms and signs of meningoencephalitis. They complained of fever, severe headaches, chills, malaise, anorexia, pain or stiffness of the neck or both, myalgia, photophobia, nausea, vomiting, drowsiness and confusion. In some patients vomiting, tiredness, sleepiness and depression persisted for several weeks after discharge from hospital. Cerebrospinal fluid (CSF) was abnormal in patients with meningoencephalitis: protein values were normal or moderately elevated and the cellular response was mainly lymphocytic; glucose values were within normal limits. In fatal cases the brain showed the typical histologic features of viral encephalitis — perivascular cuffing and microglial proliferation (N.B., Rewcastle, M. Dietrich, M.J.E. Oxley: personal communications, 1975).

### Virologic investigation

#### Methods

Serum samples from 472 patients suspected of having St. Louis encephalitis (SLE), 420 of whom were from areas thought to be involved in the outbreak, were submitted to the National Arbovirus Reference Service from all parts of the province of Ontario. One CSF and three brain specimens were also received for viral studies. Investigations were confined to tests for arboviruses on the serum samples and attempts to isolate virus from the brain and CSF specimens.

Control reagents and antigens of encephalitis-associated eastern equine encephalomyelitis (EEE), western equine encephalomyelitis (WEE), Powassan (POW) and SLE viruses isolated previously in Canada were prepared in suckling mouse brain by the methods described by Clarke and Casals.<sup>1</sup> Antigen to California encephalitis (CAL)

From the National Arbovirus Reference Service, the department of medical microbiology, faculty of medicine, University of Toronto, and the Niagara Regional Health Unit, St. Catharines, Ont.

Reprint requests to: Dr. L. Spence, Department of medical microbiology, Banting Institute, 100 College St., Toronto, Ont. M5G 1L5

virus and parallel control material were prepared from vero cell cultures.

Hemagglutination inhibition (HI) tests were performed by the method of Clarke and Casals<sup>1</sup> modified to a microtitre technique described by Sever.<sup>2</sup> Four hemagglutinating (HA) units of each of EEE, WEE, POW and CAL antigens were used routinely in the HI test; 8 HA U of SLE antigen were used in an attempt to eliminate the nonspecific inhibitory reactions obtained sometimes with this antigen.

Complement fixation (CF) tests were carried out by a modification of the microtitre method described by Sever<sup>2</sup> with 2 U of antisherp hemolysin, 2 U of complement and 4 U of antigen; the sheep cell concentration was reduced to 0.4% to provide a more sensitive test.

Attempts to isolate virus were carried out by inoculating 0.02 ml of CSF or brain suspension (20% brain in phosphate-buffered saline containing 0.75% bovalbumin) intracerebrally into suckling mice. The mice were observed for 14 days for evidence of illness.

## Results

In the HI tests (Table I) none of the serum samples reacted with EEE and WEE antigens. Serum from 33 patients showed low-titre antibody responses to CAL antigen; however, none of the positive serum reacted by CF with CAL antigen, and diagnostic increases in titre of the antibody were not demonstrated by HI. Twelve serum samples gave positive HI reactions with POW antigen, but all 12 reacted at higher titres with SLE antigen; thus the patients were presumed to be infected with SLE virus, which is antigenically related to Powassan virus — hence, cross-reactions can be expected in serologic testing. Serum samples from 82 patients were positive for SLE by HI testing; 65 of these were also positive for SLE by CF testing.

Cases of infection were considered confirmed if a fourfold increase or decrease in antibody titre was demonstrated by testing paired serum samples by CF or HI, or if a single sample had a titre of 1:32 or higher by the CF test. Thus 63 cases of SLE were confirmed serologically: in 20 there was a fourfold increase in titre; in 2, a fourfold decrease in titre; and in 41, a CF titre of 1:32 or greater in a single serum sample or in serial samples. Representative antibody titres in five confirmed cases during the outbreak are presented in Table II.

Antibodies to SLE were demonstrated by HI testing in 19 patients in whom the criteria for diagnosis of SLE infection were not met. Most of these patients had HI titres of 1:10, which could have been either nonspecific reactions or the result of past exposure to a group B arbovirus. Two of the 19 also had antibodies to SLE by CF testing but at titres of less than 1:32. Diagnostic antibody titres of 1:32 or greater were not found even though more than one serum specimen was tested.

Serologically confirmed cases of SLE originated in the following localities: Windsor, Sarnia, Chatham, Hamilton, Toronto, Lincoln, St. Catharines, Welland and Niagara Falls. In addition, one confirmed case was found in northern Ontario (Espanola) but the patient had arrived recently from Ohio, where she was thought to have acquired the disease. Many of the patients were over 40 years of age and deaths occurred only in this group.

Included among the serologically confirmed cases were two fatal cases. In a third fatal case the serum showed antibody responses to SLE antigen by both CF and HI testing, with twofold increases in antibody titre in samples taken 1 day apart. No more samples were available in this case; however, presumptive serologic findings combined with clinical and pathological

signs consistent with viral encephalitis confirmed the diagnosis of SLE (L.A. Hatch: personal communication, 1975).

Another case of SLE was diagnosed by the isolation of virus from brain tissue; this was one of the three such specimens tested. The virus was identified in a neutralization test in suckling mice inoculated intraperitoneally. No arboviruses were isolated from CSF.

## Discussion

SLE virus, first isolated in the United States in 1933,<sup>3</sup> has been responsible for numerous outbreaks of human disease in that country,<sup>4,5</sup> including an extensive outbreak in at least 25 states during 1975.<sup>6</sup> This virus was first isolated in Canada from *Culex tarsalis* mosquitoes collected in Weyburn, Sask. in 1971,<sup>7</sup> but antibody surveys<sup>8-11</sup> suggested evidence for the presence of SLE virus in Manitoba, Alberta and British Columbia in the past. The outbreak in Ontario is the first recognized outbreak of SLE in Canada and may reflect a northern extension of the large SLE outbreak that occurred in the United States during the same year.<sup>6</sup> This is also the first recorded outbreak of arbovirus encephalitis in humans in Ontario. It is not yet possible to conclude that the virus will persist in this province but further investigations are planned to determine whether it will.

This outbreak should alert physicians to the possibility of arbovirus infection in patients with aseptic meningitis or encephalitis. Any patient may be the first with SLE in an outbreak and early identification of the etiologic agent is desirable in order that appropriate control measures may be instituted.

Facilities for diagnosing arbovirus infections are now available at many of the provincial public health laboratories and at the National Arbovirus Reference Service in Toronto. The most use-

**Table I—Results of hemagglutination inhibition (HI) and complement fixation (CF) tests on single or serial serum samples from 472 patients with suspected St. Louis encephalitis in Ontario, 1975**

Antigen to encephalitis-associated virus	No. positive/total no. tested*	
	HI	CF
Eastern equine	0/472	NT
Western equine	0/472	NT
California	33/472	0/33
Powassan	12/472	NT
St. Louis	82/472	65/82

\*NT = not tested

**Table II—Representative titres of antibody to antigen of St. Louis encephalitis virus from five serologically confirmed cases of St. Louis encephalitis**

Patient no.	Date of onset of symptoms	Date serum collected	Titre	
			HI	CF
1	Aug. 28	Sept. 8	1:20	1:64
		Sept. 19	1:160	1:256
2	Aug. 1	Sept. 14	1:20	1:32
		Sept. 18	1:20	1:64
3	Sept. 12	Sept. 15	1:10	< 1:4
		Sept. 29	1:20	1:32
		Oct. 23	1:40	1:64
4	Aug. 20	Aug. 27	1:160	1:256
		Sept. 8	1:160	1:256
5	Sept. 16	Sept. 19	< 1:10	< 1:4
		Sept. 29	1:320	1:128
		Oct. 17	1:80	1:128

ful specimens for study are clotted blood specimens collected in a sterile container during both the acute and convalescent stages of illness. Since enteroviruses may produce aseptic meningitis, stool and CSF specimens should also be submitted.

We thank the physicians and medical officers of health who referred specimens to us. The cooperation of Dr. J.R. Jones, MOH for Windsor-Essex, Dr. L.M.C. Duncan, MOH for Lambton County and officials of the community health protection branch and the laboratory services branch of the Ontario Ministry of Health is gratefully acknowledged.

This work was supported in part by national health grant no. 606-1164-28(41).

## References

1. CLARKE DH, CASALS J: Techniques for haemagglutination and haemagglutination-inhibition with arthropod-borne viruses. *Am J Trop Med Hyg* 7: 561, 1958
2. SEVER JL: Application of a microtechnique to viral serological investigations. *J Immunol* 77: 320, 1962
3. *Report on the St. Louis Outbreak of Encephalitis*, public health bull no 214, Washington, US Public Health Service, 1935
4. CHIN TDY, HEIMLICH CR, WHITE RF, et al: St. Louis encephalitis in Hidalgo County, Texas. Epidemiologic features. *Public Health Rep* 72: 512, 1957
5. LUBY JP, SULKIN SE, SANFORD JP: The epidemiology of St. Louis encephalitis: a review. *Annu Rev Med* 20: 329, 1969
6. CDC tallies up totals of encephalitis epidemic. *JAMA* 234: 693, 1975
7. BURTON AN, McLINTOCK J, FRANCY DB: Isolation of St. Louis encephalitis and Cache Valley viruses from Saskatchewan mosquitoes. *Can J Public Health* 64: 368, 1973
8. DONOVAN CR, BOWMAN M: Some epidemiological features of poliomyelitis and encephalitis, Manitoba, 1941. *Can J Public Health* 33: 246, 1942
9. SPALATIN J, CONNELL R, BURTON AN, et al: Western equine encephalitis in Saskatchewan reptiles and amphibians, 1961-1963. *Can J Comp Med* 28: 131, 1964
10. IVERSEN JO, SEAWRIGHT H, HANSON RP: Serologic survey for arboviruses in central Alberta. *Can J Public Health* 62: 125, 1971
11. McLEAN DM, BERGMAN SKA, GODDARD EJ, et al: North-south distribution of arbovirus reservoirs in British Columbia, 1970. *Ibid*, p 120

## Zyloprim\* (allopurinol)

**Indications:** ZYLOPRIM is intended for the treatment of gout as well as primary and secondary hyperuricaemia. ZYLOPRIM is indicated in the treatment of primary or secondary uric acid nephropathy. ZYLOPRIM is especially useful in patients with gouty nephropathy, in those who form renal urate stones, and those with unusually severe disease. ZYLOPRIM is particularly effective in preventing the occurrence and recurrence of uric acid stones and gravel. ZYLOPRIM is useful in the therapy and prophylaxis of tissue urate deposition, renal calculi and for acute urate nephropathy in patients with neoplastic disease who are particularly susceptible to hyperuricaemia and uric acid stone formation, especially after radiation therapy or the use of antineoplastic drugs.

**Contraindications:** Zyloprim should not be given to patients who are hypersensitive or who have had a severe reaction to this drug.

**Precautions and Warnings:** Acute gouty attacks may be precipitated at the start of treatment with Zyloprim in new patients, and these may continue even after serum uric acid levels begin to fall. Prophylactic administration of colchicine and a low dosage of Zyloprim are advisable, particularly in new patients and in those where the previous attack rate has been high. Zyloprim is not recommended for use during pregnancy or in women of child-bearing potential unless in the judgement of the physician, the potential benefits outweigh the possible risks to the fetus. Zyloprim should not be given to children except those with hyperuricaemia secondary to malignancy or with Lesch-Nyhan syndrome. Patients with impaired renal or hepatic functions should be carefully observed during the early stages of Zyloprim administration and the drug withdrawn if increased abnormalities in hepatic or renal functions appear.

**Uricosurics and Zyloprim:** Combined therapy of Zyloprim and uricosurics will result often in a reduction in dosage of both agents.

**Purinethol or Imuran with Zyloprim:** In patients receiving PURINETHOL\* (mercaptapurine) or IMURAN\* (azathioprine), the concomitant administration of 300-600 mg of ZYLOPRIM per day will require a reduction in dose to approximately 1/3 to 1/4 of the usual dose of mercaptopurine or azathioprine. Subsequent adjustment of doses of PURINETHOL or IMURAN should be based on therapeutic response and any toxic effects.

**Chlorpropamide with Zyloprim:** In the presence of allopurinol, there may be competition in the renal tubule for the excretion of chlorpropamide. When renal function is poor, the recognised risk of prolonged hypoglycaemic activity of chlorpropamide may be increased if ZYLOPRIM is given concomitantly.

**Coumarin anticoagulants with Zyloprim:** It has been reported that under experimental conditions allopurinol prolongs the half-life of the anticoagulant, dicumarol. The clinical significance of this has not been established, but this interaction should be kept in mind when allopurinol is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

**Adverse reactions:** Skin reactions associated with exfoliation, fever, chills, nausea and vomiting, lymphadenopathy, arthralgia and/or eosinophilia are the most common and may occur at any time during treatment. Gastrointestinal disorders were reported but may diminish if Zyloprim is taken after meals.

**Symptoms and treatment of overdose:** Overdose of allopurinol is usually manifested by nausea and vomiting. No treatment is normally required, provided the drug is withdrawn and adequate hydration is maintained to facilitate excretion of the drug. If, however, other forms of acute distress are observed, gastric lavage should be considered, otherwise the treatment is symptomatic.

**Pharmacology:** When taken orally, allopurinol is rapidly metabolized. The main metabolite is oxypurinol, which is itself a xanthine oxidase inhibitor. Allopurinol and its metabolites are excreted by the kidney, but the renal handling is such that allopurinol has a plasma half-life of about one hour, whereas that of oxypurinol exceeds 18 hours. Thus, the therapeutic effect can be achieved by a once-a-day dosage of ZYLOPRIM in patients taking 300 mg or less per day.

**Dosage and administration:** ZYLOPRIM, administered orally should be divided into 1 to 3 daily doses. Daily doses up to and including 300 mg may be taken once daily after a meal. Divided doses should not exceed 300 mg. The minimum effective dose is 100 to 200 mg. The average is 200 to 300 mg/day for patients with mild gout, 400 to 600 mg/day for moderately severe tophaceous gout, and 700 to 800 mg/day in severe conditions. The maximal recommended dose is 800 mg per day in patients with normal renal function.

Treatment with 600 to 800 mg daily for two or three days prior to chemotherapy or x-irradiation is advisable to prevent uric acid nephropathy. Treatment should be continued at a dosage adjusted to the serum uric acid level until there is no longer a threat of hyperuricaemia and hyperuricosuria. It is essential that a daily urinary output of two litres or more be maintained during ZYLOPRIM therapy, and neutral or alkaline urine is desirable.

**Children:** For the treatment of secondary hyperuricaemia associated with malignancies and in the Lesch-Nyhan syndrome, ZYLOPRIM should be given in doses of 10 mg/kg/day. The response should be evaluated after approximately 48 hours by monitoring serum uric acid and/or urinary uric acid levels and adjusting the dose if necessary.

**Presentation:** ZYLOPRIM 100 mg scored white tablets. Bottles of 100 and 500 tablets; Code: Wellcome U4A. ZYLOPRIM 300 mg scored peach coloured tablets. Bottles of 100 tablets. Code: Wellcome C9B.

Product Monograph available on request.

W 5014  
\*Trade Mark



# Alpha Keri\* Keri\* for dry skin care

AVAILABLE AS BATH OIL IN  
120 ML, 227 ML OR 454 ML  
BOTTLES

AVAILABLE IN 184 ML, 369  
ML OR 568 ML BOTTLES  
WITH DISPENSER

\*T.M. Auth. User For Full Prescribing Information Consult Your C.P.S.

**WESTWOOD**  
PHARMACEUTICALS  
BELLEVILLE, ONTARIO K8N 5E9



Burroughs Wellcome Ltd.

LaSalle, Qué.