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AMPICILLIN COMPARED WITH PENICILLIN  
AND CHLORAMPHENICOL COMBINED IN THE  
TREATMENT OF BACTERIAL MENINGITIS

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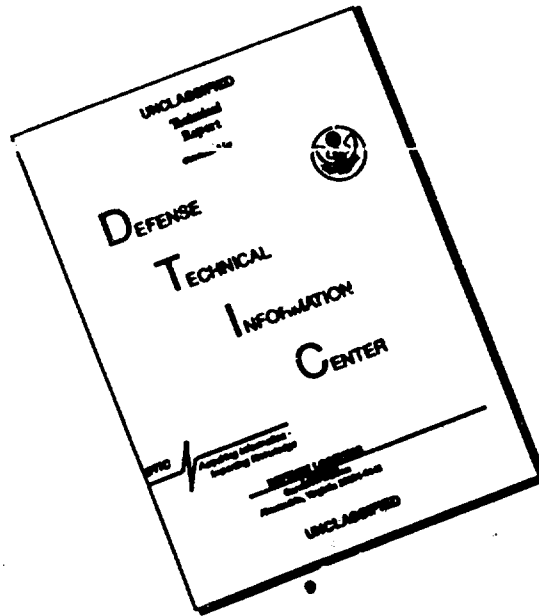
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## AMPICILLIN COMPARED WITH PENICILLIN AND CHLORAMPHENICOL COMBINED IN THE TREATMENT OF BACTERIAL MENINGITIS<sup>11</sup>

by

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### Introduction

Bacterial meningitis is endemic in the United Arab Republic. The peak seasonal incidence occurs in late summer and early spring of each year. The main causative organisms responsible for the disease are: *Neisseria meningitidis*, *Diplococcus pneumoniae* and *Haemophilus influenzae* (Hassan & Abdel Wahab, 1969).

Sulphonamides have in the past been used in Egypt in the treatment of meningococcal meningitis and for the eradication of the meningococcal carrier state.

During the past few years, however, meningococcal isolates, resistant to sulphonamides have been reported from various parts of the world (Millar *et al.*, 1963; Ivler *et al.*, 1964; Leedom *et al.*, 1965; Alexander *et al.*, 1968). In 1967, Sanborn (1969) found that 30% of the meningococcal strains isolated in the U.A.R. were resistant to sulphonamides. Subsequent studies have shown this percentage to have increased yearly to a present level of approximately 80%. Sulphonamides therefore can no longer be relied upon in the treatment of meningococcal meningitis unless sensitivity tests show the organisms to be sensitive to them.

Penicillin given parenterally in high doses is an alternative drug in the treatment of meningococcal meningitis due to sulphonamide-resistant meningococci (Lepper *et al.*, 1952; Flora, 1970).

In 20-30% of patients, organisms cannot be identified in the cerebrospinal fluid (CSF) mostly due to the use of antibiotics before admission (Carpenter & Petersdorf, 1962; Dalton & Allison, 1968). A combination of penicillin and chloramphenicol is often used for the initial treatment of bacterial meningitis before identification of the causative organism in order to cover those organisms not sensitive to penicillin alone. The drug regimen may be modified when culture and sensitivity results are available. Owing to the complications of a multiple drug regimen, especially one including chloramphenicol (Jawetz *et al.*, 1951; Wallace *et al.*, 1967), the use of a single non-toxic drug would definitely be desirable. Ampicillin (*α*-aminobenzyl penicillin) has been found to be highly effective *in vitro* against strains of *N. meningitidis*, *D. pneumoniae* and *H. influenzae* (Stewart *et al.*, 1961; Klein & Finland, 1963).

The drug yields high blood and CSF levels when given parenterally and has a low incidence of side effects (Turk *et al.*, 1964; Thrupp *et al.*, 1965; Barrett *et al.*, 1966).

As part of a general project to determine the aetiological agents responsible for acute central nervous (CNS) infections, a treatment study was initiated to evaluate the use of ampicillin as a single drug in the treatment of meningitis and to compare it with a regimen employing penicillin and chloramphenicol combined.

### Materials and Methods

This study took place during the period November 1966 to June 1968 at the Government Fever Hospital, Abbassia, Cairo. The hospital serves one half of the Cairo metropolitan area. All patients examined and suspected of having an acute CNS infection were admitted directly to a special ward.

<sup>11</sup> The opinions and assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Egyptian Ministry of Health.

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A diagnostic lumbar puncture (LP) was performed and the CSF thus obtained was examined for total and differential leucocyte count. CSF glucose and protein content were determined using standard methods (Looney & Walsh, 1939; Tonks, 1952).

All patients found to have CSF changes compatible with purulent meningitis (increased cell count with predominance of polymorphonuclear leucocytes, elevated protein, and low sugar content) were included in the treatment study. CSF specimens were also examined for bacteria by direct smear and culture.

Venous blood was obtained for bacterial culture and for complete blood count. Other clinical laboratory determinations were performed whenever indicated. Follow-up of the patients included a daily physical examination by the ward physician. Follow-up examination of spinal fluid was routinely performed on the 2nd and 7th day after admission or whenever clinically indicated. The CSF obtained was examined for cells, sugar and protein content.

On a non-selective alternating basis, patients were assigned to one of the 2 therapy regimens as they arrived on the ward. One group received ampicillin in a dose of 150 mg./kg. daily, and the second group received penicillin G in the dose of 250,000 units/kg. daily plus chloramphenicol sodium succinate 60 mg./kg. daily. These groups will henceforth be referred to as the ampicillin and the combined therapy groups respectively. All medications were given by continuous intravenous (i.v.) infusion in 2½% dextrose, 2½ saline for the first 48 hours. Thereafter, medication was given intramuscularly (i.m.) every 4 hours for the remainder of the course. Treatment was stopped after the patient had remained afebrile (rectal temperature of 37.5 or less) for 3 days unless repeat examination showed lack of improvement of CSF abnormality in which case therapy was continued until CSF findings had shown definite improvement. Therapy was always continued for a minimum of 7 days. Response to therapy was evaluated by the usual clinical criteria including disappearance of fever, improvement in mental and neurological status, and improvement in the CSF chemistry and cell count.

187 patients were included in this study. 106 were male and 81 were female. Their ages ranged from 3 months to 55 years. Ninety-four of these were treated with ampicillin and 93 with penicillin plus chloramphenicol. The 2

TABLE I  
Causative organisms in purulent meningitis.

Aetiological Agent	Number of Patients
<i>N. meningitidis</i>	60
<i>D. pneumoniae</i>	36
<i>H. influenzae</i>	15
* Miscellaneous	12
** Purulent meningitis of unknown aetiology	64
Total	187
* 4 Cases of <i>H. parainfluenzae</i>	
3 of <i>Streptococcus</i> sp.	
3 of <i>Staphylococcus</i> sp.	
1 of <i>Salmonella</i> sp.	
1 of <i>Alkaligenes</i> sp.	
**15 cases of Gram-negative diplococci	
8 of Gram-positive diplococci	
9 of Gram-negative bacilli	

groups were comparable regarding age, sex, duration of symptoms before admission and level of consciousness at the time of admission.

### Results

The causative bacteria were cultured from the CSF in 123 (66%) of the 187 patients. Of these 123 positive cultures, 60 (49%) grew *N. meningitidis*, 36 (29%) grew *D. pneumoniae*, 15 (12%) grew *H. influenzae*, and 12 (10%) grew miscellaneous organisms (Table I).

In the remaining 64 patients whose CSF cultures were negative, bacteria were seen on direct Gram stained smears from 32. Of the 64 patients with negative CSF cultures, 36 (56%) had received antimicrobial treatment before admission while of the 123 patients with positive CSF cultures, 31 (26%) had received antimicrobial treatment before admission. Duration of treatment varied from a single dose to several days' therapy.

Blood cultures were positive in only 10 patients. In all instances the identical organism was recovered from the CSF.

Response to therapy measured as mean days of treatment before defervescence was comparable in each of the 2 therapy groups being 6 days in the ampicillin group and 5.2 in the combined therapy group. Mortality was 20% in the ampicillin group and 18% in the combined therapy group. The over-all mortality was 19%. Table II shows the number of patients treated in each of the groups and the mortality according to the aetiological agent.

TABLE II Mortality according to aetiological agent and therapeutic regimen.

Aetiological Agent	Number of patients		Ampicillin treatment		Penicillin + chloramphenicol treatment	
	No. Treated	No. Died	No. Treated	No. Died	No. Treated	No. Died
<i>N. meningitidis</i>	60	7 (11%)	36	4 (11%)	24	3 (12%)
<i>D. pneumoniae</i>	36	11 (29%)	19	6 (31%)	17	5 (29%)
<i>H. influenzae</i>	15	3 (20%)	6	1 (17%)	9	2 (22%)
Miscellaneous	12	5 (41%)	7	3 (42%)	5	2 (40%)
Purulent of unknown aetiology	64	10 (15%)	26	5 (19%)	38	5 (14%)
Total no. of patients	187	36 (19%)	94	19 (20%)	93	17 (18%)

Of the patients with cultures positive for *N. meningitidis*, 4 (11%) died in the ampicillin group and 3 (12%) in the combined therapy group. In those patients with *D. pneumoniae*, 6 (31%) died in the ampicillin group and 5 (29%) in the combined therapy group. One (17%) and 2 (22%) of the patients with *H. influenzae* meningitis died in the ampicillin and the combined therapy group. Of the patients having positive cultures for organisms other than the 3 major ones, 3 (42%) died in the ampicillin group and 2 (40%) died in the combined therapy group. In the patients having purulent meningitis with negative bacterial culture, 5 (19%) died in the ampicillin group and 5 (14%) in the combined therapy group.

Of the 36 patients who died, 18 (50%) died within 24 hours after admission. Mortality was greater in the patients with a low level of consciousness at the time of admission. Death occurred in 40% of patients who were either completely unresponsive or who responded to painful stimulus only. Mortality was 16% in patients who were confused or drowsy but responded to visual and auditory stimuli. None of the patients who were alert at the time of admission died.

Localised cranial nerve dysfunction was still present in 8% of the patients in the ampicillin group, and in 9% of the combined therapy group at the time of discharge. All these patients regained function of the involved nerves on follow-up examination.

Other than skin rash not necessitating the discontinuance of therapy, there were no drug reactions in the ampicillin group. Two patients in the combined therapy group developed severe haemolytic anaemia. One died 3 days and the other 5 days after admission, despite

intensive therapy, including blood transfusion and discontinuance of the chloramphenicol. In each of these cases the haemolytic anaemia may have been a contributory cause of death. A mild skin rash attributable to penicillin was also seen in some patients in the combined therapy group.

#### Discussion

The main causative organisms of bacterial meningitis in the U.A.R., as in most parts of the world where meningitis is endemic, are *N. meningitidis*, *D. pneumoniae* and *H. influenzae*. In other series of purulent meningitis reported elsewhere in the literature the investigators were unable to culture any bacteria from the CSF in 30 to 50% of the cases (Barrett *et al.*, 1966; Carpenter & Petersdorf, 1962; Swartz & Dodge, 1965). CSF cultures are often negative in spite of organism being present on direct smear. Pre-admission treatment with antimicrobials has been suggested as the reason for the high percentage of negative CSF cultures (Dalton & Allison, 1968). In our series, 34% of the patients had no organism isolated from the CSF, yet the presenting clinical picture was that of purulent meningitis which responded to antibacterial treatment. The negative CSF cultures were probably in part due to pre-admission treatment.

The 20% mortality rate in the ampicillin group and the 18% mortality rate in the combined therapy group represent no significant difference between the 2 groups.

Other criteria used to measure response to therapy such as time required before defervescence, improvement in the mental and neurological status and the return of the

CSF findings to normal were also comparable in the 2 treatment groups. Our results compare with results of other series reported from the U.S.A. where workers have used ampicillin successfully in the treatment of purulent meningitis (Mathies *et al.*, 1965; Barrett *et al.*, 1966; Fleming *et al.*, 1966).

The low incidence of mild reactions and the absence of serious toxic reactions in the ampicillin group are in agreement with the findings of Barrett and colleagues (1966) and Fleming and colleagues (1966).

The 2 cases of haemolysis occurring in the combined therapy group may have been secondary to the administration of chloramphenicol and may have contributed to the death of the patients.

In summary, when judged by mortality, morbidity, or neurological complications, ampicillin appears as effective as the combination of penicillin and chloramphenicol for the treatment of purulent meningitis. Owing to the potential toxicity of chloramphenicol as well as the simplicity of administering one drug rather than 2, ampicillin is preferable to the penicillin-chloramphenicol combination.

#### Summary

This is a prospective treatment study of 187 patients with purulent meningitis admitted to the Abbassia Fever Hospital, Cairo, U.A.R.

The causative organism was grown from the spinal fluid in 66% of the cases. Of the culture positive cases, 49% were due to *N. meningitidis*, 29% to *D. pneumoniae*, 12% to *H. influenzae* and 10% to miscellaneous organisms. The data indicate that these are the predominant organisms causing meningitis in the U.A.R. and that ampicillin is an effective single drug in the treatment of bacterial meningitis.

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#### Bibliography

- Alexander, C. E., Sanborn, W. R., Cherriere, G., Crocker, W. H., Jr., Ewald, P. E. & Kay, C. R. (1968). *Science*, Washington, Sept. 6th, v161, 1019.
- Barrett, F. F., Eardley, W. A., Yow, M. D. & Leverett, H. A. (1966). *J. Pediat.*, v69, 343-353.
- Carpenter, R. R. & Petersdorf, R. G. (1962). *Am. J. Med.* New York, v33, 262-275.
- Dalton, H. P. & Allison, M. J. (1968). *Am. J. Clin. Path.*, v49, 410-413.
- Fleming, P. C., Murray, J. D. M., Fujiwara, M. W., Prichard, J. S. & McNaughton, G. A. (1966). *Antimicrob. Agents Chemother.*, pp. 47-52.
- Ikora, G. C. (1970). *Minn. Med.*, v53, 315-317.
- Hassan, A. & Abd el Wahab, M. F. (1969). *J. Egypt. Publ. Hlth Ass.*, v44, 246-253.
- Ivler, D., Leedom, J. M., Thrupp, L. D., Wehrle, P. F., Portnoy, B. & Mathies, A. W., Jr. (1964). *Antimicrob. Agents Chemother.*, pp. 444-450.
- Jawetz, E., Gunnison, J. B., Speck, R. S. & Coleman, V. R. (1951). *Arch. Intern. Med.*, v87, 349-359.
- Klein, J. O. & Finland, M. (1963). *Am. J. Med. Sci.*, v245, 544-555.
- Leedom, J. M., Ivler, D., Mathies, A. W., Jr., Thrupp, L. D., Portnoy, B. & Wehrle, P. F. (1965). *New Engl. J. Med.*, v273, 1395-1410.
- Lepper, M. H., Dowling, H. F., Wehrle, P. F., Blatt, N. H., Spies, H. W. & Brown, M. (1952). *J. Lab. Clin. Med.*, v40, 891-900.
- Looney, J. M. & Walsh, A. I. (1939). *J. Biol. Chem.*, v127, 117-121.
- Mathies, A. W., Jr., Leedom, J. M., Thrupp, L. D., Ivler, D., Portnoy, B. & Wehrle, P. F. (1965). *Antimicrob. Agents Chemother.*, pp. 610-617.
- Millar, J. W., Siess, E. E., Feldman, H. A., Silverman, C. & Frank, P. (1963). *J. Am. Med. Ass.*, v186, 139-141.
- Sanborn, W. R. (1969). *J. Egypt. Publ. Hlth Ass.*, v44, 356-368.
- Stewart, G. T., Coles, H. M. T., Nixon, H. H. & Holt, R. J. (1961). *Br. Med. J.*, v2, 200-206.
- Swartz, M. N. & Dodge, P. R. (1965). *New Engl. J. Med.*, v272, 725-731.
- Thrupp, L. D., Leedom, J. M., Ivler, D., Wehrle, P. F., Portnoy, B. & Mathies, A. W. (1965). *Antimicrob. Agents Chemother.*, pp. 206-213.
- Tonks, D. B. (1952). *Am. J. Clin. Path.*, v22, 1009-1017.
- Turek, M., Anderson, K. N., McKee, W. M., Shulman, J. A., Smith, R. H. & Petersdorf, R. G. (1964). *Antimicrob. Agents Chemother.*, pp. 220-225.
- Wallace, J. F., Smith, R. H., Garcia, M. & Petersdorf, R. G. (1967). *J. Lab. Clin. Med.*, v70, 408-418.