

# Two dose Augmentin treatment of acute gonorrhoea in men

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**SUMMARY** We studied 192 men with acute gonococcal urethritis, 97 of whom received two oral doses of Augmentin (amoxycillin 3 g and clavulanic acid 250 mg) separated by a four hour interval; the remaining 95 received 2 g kanamycin in a single intramuscular injection. Of the patients treated with Augmentin, 93 (95.9%) were cured, which was significantly more than the 83 (87.4%) patients treated with kanamycin. Augmentin was equally effective in the treatment of penicillinase producing *Neisseria gonorrhoeae* (PPNG) and non-PPNG infections, the cure rates for which were 96.6% and 95.6% respectively.

## Introduction

The introduction of sulphonamides in 1937 and the use of penicillin since the second world war have failed to reverse the continuing worldwide increase in the incidence of gonorrhoea. Although the increase may be partly explained by a change in moral attitudes, two microbiological factors play a significant part. These are a gradual reduction in sensitivity of the gonococcus to penicillin and the emergence of  $\beta$ -lactamase, or penicillinase producing, *Neisseria gonorrhoeae* (PPNG). PPNG strains, which originated in West Africa and South East Asia, were first reported in 1976 in England and the United States of America.<sup>1,2</sup> Since then, these strains have become well established in their regions of origin and have spread worldwide.<sup>3</sup> Their ability to disseminate internationally threatens effective treatment of gonorrhoea with penicillin and other  $\beta$ -lactam antibiotics.

There have been two approaches to the  $\beta$ -lactamase problem. One has been the development of antimicrobials stable to  $\beta$ -lactamase, and the other has been the search for inhibitors of  $\beta$ -lactamase. Clavulanic acid isolated from *Streptomyces clavuligerus* is a potent inhibitor of  $\beta$ -lactamase.<sup>4</sup> In combination with amoxycillin, it extends the antibacterial activity of amoxycillin to include  $\beta$ -lactamase producing strains, which are otherwise resistant. Earlier studies have shown that  $\beta$ -lactamase producing strains of *N gonorrhoeae* resistant to

amoxycillin at concentrations of 4-64 mg/l are susceptible to a combination of amoxycillin and clavulanic acid.<sup>5,6</sup> Augmentin is a formulation comprising amoxycillin and the potassium salt of clavulanic acid. Both components are well absorbed by the oral route. Peak serum concentrations of 6.06 mg/l of amoxycillin and 4.22 mg/l of clavulanic acid were obtained after 1½ hours in patients receiving Augmentin 750 mg (amoxycillin 500 mg plus clavulanic acid 250 mg) by mouth.<sup>7</sup>

Augmentin appeared to be worth considering for the treatment of gonorrhoea in Singapore, where PPNG strains account for nearly 35% of all gonococcal strains isolated. Preliminary studies (unpublished) on the use of a single dose of Augmentin in the treatment of gonorrhoea showed a failure rate of about 29% for PPNG infections and 8% for non-PPNG infections. Antibiotic susceptibility tests showed no cases of in vitro resistance. Hence it was postulated that the poor results obtained with PPNG infections compared with non-PPNG infections were due to the short duration of effective clavulanic acid concentrations present in body fluids.

In this study, therefore, we chose to use two doses of Augmentin (amoxycillin 3 g plus clavulanic acid 250 mg) separated by a four hour interval.

## Patients and methods

### STUDY POPULATION

This study was conducted at the outpatient department of this hospital from December 1982 to May 1983, and 200 men with acute gonococcal urethritis were recruited into the trial. Patients with a history of

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penicillin allergy or who had received antimicrobials over the 72 hours preceding the start of the study were excluded.

#### DIAGNOSIS

Gonorrhoea was diagnosed on the finding of Gram negative intracellular diplococci in stained smears and was subsequently confirmed on culture. Gonococcal isolates were recognised by their colonial morphology on modified Thayer-Martin medium, oxidase reaction, and Gram stained microscopic appearance. Penicillinase production was tested for in all isolates by the paper acidometric method.<sup>8</sup>

#### TREATMENT

Half the patients received two doses of Augmentin as described below, while the remaining 100 received 2 g of kanamycin in a single intramuscular injection. Augmentin was administered in a sachet containing amoxycillin 3 g and clavulanic acid 250 mg. The contents of the sachet were dissolved in a glass of water and were administered under supervision. The patient was then instructed to take the second dose after a four hour interval and given a second sachet with the time for taking the second dose indicated.

#### FOLLOW UP AND TESTS OF CURE

All patients were assessed on days 5 and 14 after treatment. Urethral smears and cultures were obtained at each visit. Treatment was assumed to have failed if the culture remained positive on day 5 and the patient denied having had further sexual intercourse. If gonococci were isolated on day 14 and the patient admitted having had sexual intercourse, then reinfection was assumed. The Venereal Diseases Research Laboratory (VDRL) test was performed before treatment and at six weeks and three months afterwards.

#### Results

##### TREATMENT RESPONSE

The results of treatment are shown in table I. Eight patients defaulted from follow up and were therefore excluded, leaving 192 patients for assessment.

Out of 97 cases treated with Augmentin there were four failures, giving an overall cure rate of 95.9%. Of 29 PPNG infections 28 (96.6%) were eradicated, compared with 65 (95.6%) of 68 non-PPNG infections. Kanamycin successfully eradicated 20 (83.3%) of 24 PPNG infections and 63 (88.7%) of 71 non-PPNG infections, giving an overall success rate of 87.4%. Overall, Augmentin was significantly ( $\chi^2=4.55$ ;  $p<0.05$ ) more effective than kanamycin. No side effects to Augmentin were recorded.

TABLE I Treatment response to two dose Augmentin

	Total treated	No (%) cured	No (%) failed
Augmentin (amoxycillin 3 g + clavulanic acid 250 mg) two 4 hourly oral doses			
PPNG	29	28 (96.6)	1 (3.4)
Non-PPNG	68	65 (95.6)	3 (4.4)
Total	97	93 (95.9)	4 (4.1)
Kanamycin 2 g intramuscularly			
PPNG	24	20 (83.3)	4 (16.7)
Non-PPNG	71	63 (88.7)	8 (11.3)
Total	95	83 (87.4)	12 (12.6)

#### ANTIBIOTIC SUSCEPTIBILITY

Tests for antibiotic susceptibility to Augmentin were performed on 29 PPNG and 68 non-PPNG isolates. The minimum inhibitory concentrations (MICs) were measured by the agar plate dilution method previously described.<sup>9</sup> Augmentin (amoxycillin and clavulanic acid in a 2:1 ratio) was used in doubling dilutions from 8 mg/l to 0.125 mg/l.

Table II shows that PPNG isolates were less susceptible than non-PPNG strains, with MICs of 1-4 mg/l compared with 0.125-4 mg/l. The geometric mean MICs for PPNG and non-PPNG isolates were 2.098 and 0.571 mg/l respectively. The distribution of their MICs differed significantly ( $\chi^2=43.60$ ;  $p<0.001$ ).

MICs for isolates taken before and after treatment from four patients whose treatment failed were identical or differed by only one dilution. Of these, three were non-PPNG isolates with MICs of 0.25, 0.25, and 0.5 mg/l before treatment, and one was a PPNG isolate with an MIC of 4 mg/l before treatment.

TABLE II Susceptibility of *N gonorrhoeae* to Augmentin

Strains (No)	No inhibited by MICs (mg/l) of:					
	0.125	0.25	0.5	1	2	4
PPNG (29)				6	15	8
Non-PPNG (68)	1	22	21	14	7	3

$\chi^2=43.60$ ;  $p<0.001$

#### Discussion

PPNG strains were first isolated in Singapore late in 1976.<sup>10</sup> Since then they have been found increasingly, and in 1982 accounted for 34.5% of all gonococcal strains isolated here. Clearly, an antibiotic effective against both PPNG and non-PPNG strains is potentially useful in the treatment of gonorrhoea in Singapore.

We achieved an overall cure rate of 95.9% with two doses of Augmentin (amoxicillin 3 g and clavulanic acid 250 mg) separated by a four hour interval. This regimen was equally effective for PPNG and non-PPNG infections, the cure rates for which were 96.6% and 95.6% respectively. No side effects were recorded. This study therefore confirms that Augmentin used as above is very effective against all strains of *N gonorrhoeae*. The results compare favourably with those obtained with spectinomycin<sup>11</sup> and cefotaxime.<sup>12</sup> Furthermore, Augmentin can be safely and easily administered (orally).

Surprisingly, initial studies using single dose Augmentin (amoxicillin 3 g and clavulanic acid 250 mg) resulted in cure rates of only 71.4% for PPNG infections and 92.3% for non-PPNG infections. It was postulated that the duration of an effective clavulanic acid serum concentration with a single dose was insufficient to provide maximum inhibition of penicillinase. The significantly improved cure rate obtained with the two dose Augmentin regimen indirectly lends support to the above hypothesis.

The poor results of single dose Augmentin treatment are, however, difficult to explain conclusively. A study conducted in the Philippines by Lao *et al* using Augmentin (amoxicillin 3 g and clavulanic acid 125 mg) for the treatment of PPNG infections recorded a cure rate of 92%.<sup>13</sup> Another study conducted in Amsterdam by Tio *et al* using Augmentin (amoxicillin 3 g and clavulanic acid 0.5 g) plus probenecid 1 g resulted in a similar cure rate of 93.6% for PPNG infections.<sup>14</sup> What then, might be the reasons for the differences in cure rates between our studies and studies conducted elsewhere? Differences in the antimicrobial susceptibility of PPNG strains may be a factor, as the authors mentioned did not report the MICs for their isolates. Another factor may be individual variation in the pharmacokinetics of clavulanic acid in the body. A third possibility is that strains of PPNG found in Singapore may produce more penicillinase, and therefore require more clavulanic acid to neutralise it. Further studies are necessary to provide an answer.

In conclusion, two doses of Augmentin (amoxicillin 3 g and clavulanic acid 250 mg)

separated by a four hour interval constitute an effective treatment for gonorrhoea. Augmentin permits simple oral treatment and is well tolerated. Its use should be considered in areas where PPNG is prevalent.

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