A randomized, prospective study comparing once-daily gentamicin versus thrice-daily gentamicin in the treatment of puerperal infection


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Once-daily gentamicin dosing with twice-daily clindamycin dosing for peripartum uterine infection in patients with puerperal endometritis or with chorioamnionitis in labour. The experimental group received gentamicin 4 mg/kg intravenously every 24 hours with clindamycin 1,200 mg intravenously every 12 hours.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Patients with puerperal endometritis or with chorioamnionitis in labour. The patients met the following criteria: two temperatures of 100.4 degree F or higher 6 hours apart excluding the first 12 postpartum hours, a single temperature of 102 degree F or higher in the first 12 postpartum hours, a diagnosis of chorioamnionitis in labour thought to require postpartum prophylactic antibiotic therapy, or a diagnosis of postpartum endometritis after initial discharge from hospital. Additional supporting factors for the diagnosis of postpartum endometritis were uterine tenderness, foul-smelling lochia, an elevated white blood cell count, and maternal tachycardia. Patients were excluded if they had a baseline serum creatinine level greater than 1.5 mg/dl, extrapelvic sources of infection, and allergy or hypersensitivity to either drug.

Setting
Hospital. The economic analysis was carried out in the USA.

Dates to which data relate
Effectiveness and resource use data corresponded to patients enrolled in the study between 1 July 1994 and July 1996. The price year was not explicitly reported.

Source of effectiveness data
The evidence for the final outcomes was based on a single study.

Link between effectiveness and cost data
Costing was conducted on the same patient sample as that used in the effectiveness analysis. However, it is not clear whether costing was performed prospectively or retrospectively.
Study sample
Power calculations were used to determine the sample size: with an alpha less than 0.05, power of 80%, and an assumed cure rate of 90% for the conventional treatment, 136 patients in each study group were needed to detect a 15% difference in the two treatment regimens. Initially, a total of 299 patients were enrolled in the study, of whom 27 were excluded for protocol violations. 135 patients with a mean (median) age of 23.3 (21.1) years were randomised to the experimental group and 137 patients with a mean (median) age of 22.5 (21.4) years to the conventional group.

Study design
The study was a randomised controlled trial, carried out in single centre. The duration of the follow-up appears not to have been explicitly specified; it was only referred to as being several weeks after discharge. Loss to follow-up was 27 patients who were excluded because of protocol violation, of whom 9 did not meet enrolment criteria, 7 had inappropriate antibiotic changes before receiving 72 h of the assigned treatment regimen, 8 patients never received the study medications, and 3 patients had antibiotics discontinued before cure was achieved. Before enrolment each patient underwent a history and physical examination and a laboratory evaluation comprising a complete blood cell count with differential, a urinalysis with culture, and a baseline serum creatinine concentration. Treatment assignments were randomly generated by a computer. Physicians were not blinded with respect to the dosing regimen.

Analysis of effectiveness
The principle used in the analysis of effectiveness appears to have been treatment completers only. The primary clinical outcomes were cure rates, mean length of treatment, relapse, nephrotoxicity, and gentamicin peak and trough levels. Subgroup analysis was also performed. The study groups were comparable in terms of baseline demographic and clinical characteristics, except for mode of delivery. Multiple logistic regression analysis was used to control for confounding variables (mode of delivery and reason for treatment).

Effectiveness results
Cures were obtained in 94.1% of patients in the experimental group and 87.6% of patients in the conventional group, \( p=0.06 \). There were no relapses in either treatment group. The mean (median) length of treatment was 2.1 (2.0) days in the experimental arm versus 2.5 (2.0) in the conventional arm, \( p=0.004 \). There was no permanent nephrotoxicity in either group; transient nephrotoxicity occurred in one patient in the once-daily gentamicin group. The mean gentamicin peak values were 5.3 mg/dl (conventional) versus 12.8 mg/dl (experimental), \( p=0.001 \). The mean trough levels were 0.9 mg/dl in the conventional group and 0.5 mg/dl in the experimental group, \( p=0.001 \). In the subgroup analysis, in patients with postpartum endometritis, 94.3% (66 of 70) of the patients in the experimental group were cured by the assigned treatment regimen versus 81.7% (58 of 71) in the conventional group, \( p=0.02 \). No statistically significant difference was observed in terms of cure rates when the subset of patients with chorioamnionitis were compared between the two groups.

Clinical conclusions
Initial analysis of the data strongly supported the hypothesis that the experimental regimen was as efficacious as the conventional dosing interval regimen for the treatment of puerperal infection. In fact, with the exception of the chorioamnionitis subset, the experimental treatment resulted in a higher percentage of cures than the conventional treatment did in every other subset that the authors examined. However, after controlling for potential confounding, the difference in cure rates between the two study groups in the endometritis subset was not statistically different.

Measure of benefits used in the economic analysis
No summary benefit measure was identified in the economic analysis, and only separate clinical outcomes were reported.

Direct costs
Costs were not discounted due to the short time frame of the cost analysis. Some quantities were reported separately.
from the costs. Cost items were reported separately. The cost analysis covered the costs of medication and intravenous administrative charges. The perspective adopted in the cost analysis was not stated. The source of cost data was the pharmacy charges to the patient. The price year was not explicitly specified.

**Statistical analysis of costs**

It appears that the Wilcoxon rank sum test was used to detect differences between the groups in terms of costs.

**Indirect Costs**

Not considered.

**Currency**

US dollars ($).

**Sensitivity analysis**

Not conducted.

**Estimated benefits used in the economic analysis**

Not applicable.

**Cost results**

The mean total charges for antibiotic treatment for the conventional group was significantly more costly at $442.49 per patient versus $250.79 per patient for the experimental group, (p=0.0001).

**Synthesis of costs and benefits**

Costs and benefits were not combined.

**Authors’ conclusions**

Once-daily gentamicin dosing with twice-daily clindamycin dosing is as efficacious and safe as the thrice-daily dosing of gentamicin and clindamycin for peripartum uterine infection. The experimental regimen results in substantial cost savings. The incidence of nephrotoxicity is low.

**CRD COMMENTARY - Selection of comparators**

The strategy of using the thrice-daily dosing of gentamicin and clindamycin, as the conventional therapy in the context in question, was regarded as the comparator. You, as a database user, should consider whether this is a widely used health technology in your own setting.

**Validity of estimate of measure of effectiveness**

The internal validity of the effectiveness results is likely to be high due to the randomised nature of the study design and the power analysis performed. The study groups were comparable in terms of baseline demographic and most clinical characteristics. In order to account for confounding variables, the authors applied multiple regression analysis. However, the facts that the randomisation was not blinded and the effectiveness analysis was based on the principle of treatment completers only weaken the internal validity of the effectiveness analysis. Furthermore, as acknowledged by the authors, a weakness of the study was the altering of the dosing schedule for clindamycin and gentamicin in both patient groups. As a result, this precluded the authors from distinguishing what benefit was derived from altering the gentamicin dosing schedule from that derived from the different clindamycin dosing schedule. The study sample
appears to have been representative of the study population.

**Validity of estimate of measure of benefit**
The authors did not derive a summary measure of health benefit and, as such, the study was a cost-consequences analysis.

**Validity of estimate of costs**
Very limited details of the methods of cost estimation were given, which hinders the assessment of its quality. Patient charges were used as a proxy for costs and statistical analyses were performed on resource consumption and cost data. However it is impossible to judge whether any costs were omitted from the analysis because of the lack of detail provided on resource use and item costs. The effects of alternative procedures on indirect costs were not addressed and only direct medical costs were included in the cost analysis. In addition, the price year used by the authors, was not reported. Cost results may not be generalisable to other settings or countries.

**Other issues**
The authors' conclusions regarding the benefits from the treatment strategies under investigation appear to be reasonably justified. However, more caution should be exercised when interpreting the cost results, as they appear to be of limited transferability. Furthermore, sensitivity analysis would have been helpful in order to account for the uncertainties in the data. The issue of generalisability to other settings was not addressed, although some comparisons were made with other studies. Regarding the issue of the representativeness of the study sample of the study population, it was acknowledged that the study entrance criteria allowed some patients into the study who may not have required any antibiotic therapy, specifically patients with chorioamnionitis in labour, and patients with an isolated temperature spike of 102 degree F in the first 12 hours after vaginal delivery. It was reported that, even after the exclusion of these two groups of patients, the study still had a power of 75% to detect a 15% difference in cure rates.

**Implications of the study**
Given the low incidence of toxic troughs and the fact that the mean length of treatment is only 2.1 days, the authors questioned whether routine monitoring of gentamicin levels is necessary for the typical postpartum patient with normal renal function who responds promptly to therapy.

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None stated.

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