Comparison of ampicillin with clindamycin plus gentamicin in the treatment of postpartum uterine infection

DONALD G. POND, MD; PAUL E. BERNSTEIN, MD; KATHRYN R. LOVE, MD; JOHN R. MORGAN, PH D; HILLAR VELLAND, MD; JOHN A. SMITH, MD

A prospective randomized study of the treatment of postpartum endometritis was conducted with 43 patients. The bacterial origin of the infection was determined by uterine aspiration. Treatment was successful in 17 of the 19 patients receiving ampicillin (12 g/d) and in 21 of the 24 patients receiving clindamycin (2.4 g/d) plus gentamicin (5.1 mg/kg daily).

Une étude prospective randomisée du traitement de l'endométrite puerpérale a été réalisée chez 43 patientes. L'origine bactérienne de l'infection a été déterminée par aspiration utérine. Le traitement a été couronné de succès chez 17 des 19 patientes qui ont reçu de l'ampicilline (12 g par jour), et chez 21 des 24 patientes qui ont reçu de la clindamycine (2.4 g par jour) et de la gentamicine (5.1 mg/kg par jour).

While a number of authors have reported on the bacteria and the antibiotic susceptibility patterns associated with puerperal infections,[1] there are few authoritative guidelines for the initial choice of antibiotic regimens in such infections. Gorbach and Thadepalli[2] found clindamycin alone to be useful in mixed aerobic and anaerobic infections, but they preferred to combine this drug with an aminoglycoside. Mead and Gump[3] have used ampicillin with gentamicin or clindamycin with gentamicin for severely ill patients, and ampicillin or a cephalosporin for moderately ill patients. Ledger, Kriewall and Sweet[4] compared penicillin and kanamycin with clindamycin and kanamycin and found both regimens to be imperfect.

Our practice has been to use clindamycin and gentamicin pending bacteriologic evaluation, and in many cases we have continued this treatment to a successful conclusion. These drugs were intended to cover the Enterobacteriaceae, streptococci, staphylococci and anaerobic gram-negative rods. However, we were impressed that ampicillin also seemed effective in a number of cases treated by colleagues. Therefore, we decided to conduct a prospective randomized study comparing ampicillin given in high doses with a combination of clindamycin and gentamicin in the early empirical treatment of patients with a clinical diagnosis of postpartum endometritis.

Methods

Patient selection and assignment to therapy

At Mount Sinai Hospital, Toronto, a 441-bed teaching hospital, there are 76 obstetric beds, all for private patients. During the study interval, August 1976 to June 1977, there were 3173 deliveries, of which 2589 were vaginal, 432 were by emergency cesarean section and 152 were by elective cesarean section. Of the patients, 86 were considered for inclusion in the study and 43 were selected. Exclusions were due to inadvertent or unintentional treatment with an antibiotic regimen other than the two being studied, or to an uncertain diagnosis of pelvic infection. Other characteristics of the patients are shown in Table I. In only one

Table I—Characteristics of patients with postpartum endometritis receiving early empirical antibiotic therapy

Variable	Treatment group: Ampicillin (n = 19)	Treatment group: Clindamycin and gentamicin (n = 24)
Mode of delivery		
Vaginal	8	9
Cesarean section		
Emergency	11	12
Elective	0	3
Mean interval from rupture of membranes to delivery (hours)	8.3	8.6
Mean duration of temperature ≥ 38°C before antibiotic therapy begun (hours)	40.4	40.5

From the departments of medicine, medical microbiology, and obstetrics and gynecology, University of Toronto, and Mount Sinai Hospital, Toronto

Reprint requests to: Dr. John A. Smith, Division of microbiology, Vancouver General Hospital, 855 West 12th Ave., Vancouver, BC V5Z 1M9

patient, a member of the ampicillin group, was there another cause for the fever — a wound infection.

It was considered impractical to conduct the therapeutic and clinical assessment components of this study in a double-blind fashion.

The patients whose medical record number ended with an even digit received ampicillin, 2.0 g intravenously every 4 hours; those whose number ended with an odd digit received clindamycin, 600 mg orally every 6 hours, and gentamicin, 1.7 mg/kg of body weight intravenously every 8 hours. None of the patients had renal dysfunction. Treatment was given for a minimum of 5 days, the duration depending on the response.

Clinical assessment

All patients were assessed clinically by one individual (D.G.P.) to confirm the diagnosis of endometritis, which was based on the presence of fever (oral temperature 38°C or higher), abdominal pain, uterine or lower abdominal tenderness and subinvolution of the uterus; foul lochia was a feature in some patients. Bacteriologic data were obtained to support the diagnosis. The condition of each patient was reviewed daily and the clinical status was recorded on a protocol sheet. These data were used to evaluate the duration of illness before cure.

Bacteriologic assessment

Two types of bacteriologic sampling were used. In one method cervical swabs were obtained from the unprepared cervix through a speculum; these were taken to the laboratory in Amies' modification of Stuart's transport medium.[5] The second method was uterine aspiration. A sterile plastic catheter inside a rigid plastic outer sleeve was passed through the cervix, which had been prepared with a solution of povidone-iodine (Proviodine®) or a 1:2000 aqueous solution of chlorhexidine diacetate (Hibitane®). The uterine contents were aspirated into a 6-mL syringe attached to the catheter, placed in Amies' modification of Stuart's transport medium and transported to the laboratory. The interval between obtaining the sample from the patient and inoculating the appropriate culture media did not exceed 5 minutes.

All samples were cultured aerobically and anaerobically, and isolates were identified by standard bacteriologic methods; the anaerobic techniques have been described elsewhere.[6] Antibiotic sensitivity testing of aerobic bacteria was by either the Kirby-Bauer[7] or the Autobac I[8] method, and of anaerobic bacteria was by the agar dilution method of Sutter, Vargo and Finegold.[9]

Bacteriologic evaluation was done at the initiation of treatment, and subsequent cultures were not done provided the patient responded to treatment. No attempt was made to culture *Mycoplasma* species. Failure to respond necessitated repeated bacteriologic testing.

Blood samples were drawn once for culture from all patients before antibiotic therapy was begun.

Response to treatment

Daily clinical assessment was performed with the intention of changing to the alternative regimen when a patient did not show satisfactory clinical response to treatment or when the bacteriologic findings necessitated a change in therapy. The decision to consider treatment as having failed was made by one individual (J.A.S.), who did not know the antibiotic regimen for each patient. This judgement was based on persistence of a temperature of 38°C or higher together with at least two of the following features: subinvolution of the uterus, excessive or foul lochia, and abdominal pain or tenderness.

Results

Seventeen cervical swabs, compared with 20 uterine samples, yielded pure cultures of single bacteria. Moreover, one pure culture from a cervical swab and six pure cultures from uterine samples were associated with multiple bacterial isolates from the other site. For these reasons, only the uterine samples were included in the analyses.

The bacteria recovered from patients in the two treatment groups, including the isolates resistant to one or both of the drugs in the initial treatment regimen, are shown in Table II. No bacteria were cultured from the uterine contents of six patients who received ampicillin, although pus cells and gram-positive cocci or gram-negative rods were seen in smears of the uterine aspirates; *Staphylococcus epidermidis* was cultured from the cervical swabs of one of the six. Similarly, no bacteria were cultured from the uterine contents of four patients who received clindamycin, although pus cells were seen in smears of the uterine aspirates of all four, and gram-negative rods were seen in those of three; *Bacteroides* sp. sensitive to clindamycin was cultured from the cervical swabs of two of the four.

The success rate for ampicillin therapy (89%) was similar to that for clindamycin and gentamicin therapy (88%). The success of ampicillin therapy was uniformly predictable from the results of the susceptibility tests. The two treatment failures were related to penicillinase production by *S. aureus*. The success of clindamycin and gentamicin therapy was also correlated with antimicrobial susceptibility patterns except in the patients with *Streptococcus faecalis* or other enterococcal infection. In one case there was no evidence from Gram's staining of any other pathogen, but in two cases there were associated bacteria causing infection, including a *Bacteroides* sp. that may have been the main pathogen. The treatment failures with clindamycin and gentamicin were in one patient with a mixed *S. faecalis* and *Escherichia coli* infection (the *S. faecalis* was resistant to both drugs and the *E. coli* was sensitive to gentamicin) and in two patients with group B β-hemolytic streptococcal infection (one may have responded more to the release of 75 mL of pus from the uterine cavity during repeat uterine aspiration than to the change to ampicillin therapy).

Details of the timing of antibiotic therapy in the five patients in whom treatment was changed are outlined in Table III. One patient inadver-

Table II—Bacteria isolated from uterine contents, efficacy of antibiotic therapy and antibiotic susceptibility

Bacteria isolated	Treatment group; outcome; antibiotic susceptibility*											
	Ampicillin (n = 19)						Clindamycin and gentamicin (n = 24)					
	Success			Failure			Success			Failure		
	S	M	R	S	M	R	S	M	R	S	M	R
Group B β-hemolytic streptococci	2	–	–	–	–	–	4	–	–	2	–	–
Staphylococcus aureus	1	–	–	–	–	2	1	–	–	–	–	–
Bacteroides fragilis	–	–	–	–	–	–	1	–	–	–	–	–
Bacteroides sp.	1	–	–	–	–	–	1	–	–	–	–	–
Peptococcus	1	–	–	–	–	–	2	–	–	–	–	–
Escherichia coli	–	–	–	–	–	–	2	–	–	–	–	–
Staphylococcus epidermidis	–	–	–	–	–	–	2	–	–	–	–	–
Alpha-hemolytic streptococci	2	–	–	–	–	–	–	–	–	–	–	–
Group B streptococci, *Bacteroides* sp. and *Peptococcus*	–	–	–	–	–	–	1	–	–	–	–	–
Enterococci, *Bacteroides* sp. and *Peptostreptococcus*	–	–	–	–	–	–	–	1	–	–	–	–
Streptococcus faecalis	–	–	–	–	–	–	–	–	1	–	–	–
S. faecalis and *B. fragilis*	–	–	–	–	–	–	–	1	–	–	–	–
S. faecalis and *E. coli*	1	–	–	–	–	–	–	–	–	–	1	–
Streptococcus avium	1	–	–	–	–	–	–	–	–	–	–	–
Fusobacterium sp.	1	–	–	–	–	–	–	–	–	–	–	–
Fusobacterium sp., *Clostridium* sp. and *S. epidermidis*	1	–	–	–	–	–	–	–	–	–	–	–
Total no.	11	0	0	0	0	2	14	2	1	2	1	0
No growth		6						4				

*S = all bacteria isolated were sensitive; M = mixed susceptibility (both sensitive and resistant bacteria were isolated); R = all bacteria isolated were resistant.

Table III—Details of therapy for the five patients whose condition failed to respond to the initial choice of therapy

Case no.	Bacteria isolated from uterus	Initial antibiotic regimen (and interval [days] from onset of therapy to change)	Subsequent antibiotic regimen (and interval [days] from change to clinical success)
1	Group B streptococci	Clindamycin and gentamicin (7)	Ampicillin (3)
2	*S. aureus*	Ampicillin (2)	Clindamycin and gentamicin (4)
3	Group B streptococci	Clindamycin and gentamicin (3)	Penicillin G (5)
4	Enterococci and *E. coli*	Clindamycin and gentamicin (3)	Ampicillin (3)
5	*S. aureus*	Ampicillin (0.5)	Clindamycin and gentamicin (3)

Table IV—Intervals before clinical improvement in patients successfully treated

Interval (days) after onset of therapy	Treatment group	
	Ampicillin (n = 17)	Clindamycin and gentamicin (n = 21)
Until afebrile	2.4	2.6
Until well	3.9	3.4
Until discharged	6.7	6.6

tently received penicillin G instead of ampicillin when treatment was changed.

The clinical course of patients in the two treatment groups is compared in Table IV. The mean duration of fever after the initiation of therapy was about the same in the two groups, as were the intervals until the patients were well and until they were discharged from hospital. The patient was considered afebrile when the temperature was consistently below 37.2°C.

Several points of interest were the low proportion of patients with bacteremia (5%), the low proportion with Enterobacteriaceae infection (9%) and the frequency of infection with *S. aureus* and group B streptococci (30%).

Discussion

The fact that 23 (53%) of infected patients in this study were delivered by emergency cesarean section while only 13.6% of all deliveries were in this category accords with the generally accepted view that uterine contamination and sepsis are related to a long interval between rupture of the membranes and difficult labour culminating in emergency cesarean section. By contrast, only three (7%) of the infected patients studied were delivered by elective cesarean section,

while 4.8% of all deliveries were by this method. Vaginal delivery accounted for 40% of the deliveries in the infected group and for 81.6% of all deliveries in the hospital during the study interval.

A daily record was kept of specific features including abdominal pain, uterine or lower abdominal tenderness, uterine involution and characteristics of the lochia. By paying careful attention to these records we were able to use these features, in association with temperature response, to decide about therapeutic efficacy without as much difficulty as we had expected.

Our data indicate that either of the two antibiotic regimens is appropriate in the early treatment of endometrial infection in the puerperium pending bacteriologic evaluation, provided the Gram-stained smear of the uterine contents does not suggest staphylococcal, clostridial or gonococcal infection. Such infections might indicate the use of penicillin G or a semisynthetic penicillin such as cloxacillin.

We compared the findings from the cultures of cervical swabs and uterine aspirates because we suspected that the results of cervical testing might be unreliable. Similar lack of enthusiasm for cervical swabs in endometritis was expressed by Gibbs and Weinstein.[1] We had more "sterile" samples from the uterine cavity than from cervical swabs, an observation also made by Morgan and colleagues.[10] The reason for this is not clear. Failure to aspirate from the infected site is unlikely in view of the presence of pus cells in all Gram-stained smears of uterine aspirates from these patients and gram-positive cocci and gram-negative rods in 9 of the 10 samples. More likely is loss of viability of anaerobic cocci and anaerobic gram-negative rods such as *Bacteroides* sp.

In general, the response of the patients to either antibiotic regimen was rapid. In two patients the response was slow and the treatment was changed to ampicillin in one and, inadvertently, to penicillin G in the other. Thereafter the response was rapid in both. In the patient whose condition seemed to respond poorly to the initial regimen but improved with administration of the alternative drug and aspiration of pus, we looked for antibacterial activity against group B streptococci in the uterine contents while the patient was receiving clindamycin and gentamicin therapy. We inoculated a well in an agar plate seeded with her hemolytic streptococci and noted a large zone of inhibition. We made no attempt to measure this activity. These two patients may not have represented genuine treatment failures. Perhaps the organisms were simply killed slowly.[11] Moreover, the apparent response to ampicillin might be partly attributable to the prior clindamycin and gentamicin therapy. This question requires closer study.

We included a number of bacteria in our list of isolates whose pathogenic role may be open to question. We have no way at present of assessing the significance of coagulase-negative *S. epidermidis* and α-hemolytic streptococci. Our findings with regard to *E. coli* in particular are in marked contrast to those of Sweet and Ledger,[12] who found this organism to be the predominant pathogen in endometritis at the two institutions in which they conducted their study. We have no explanation for this apparent discrepancy, although differences in sampling techniques might be the reason.

Because most of the *B. fragilis* infections were in the patients treated with clindamycin and gentamicin, there was little opportunity to evaluate the efficacy of ampicillin in the treatment of such patients. In vitro data suggest that ampicillin in high doses might be effective against *B. fragilis*,[13] but this should be confirmed by in vivo studies.

The samples of five patients yielded enterococci. There was no response to clindamycin and gentamicin therapy in the one who was infected with *S. faecalis* and *E. coli*, but there was a satisfactory response to this regimen in three other patients. Ledger and colleagues[4] found that enterococcal infections responded poorly to clindamycin and kanamycin, but Gorbach and Bartlett[14] questioned the pathogenic potential of this group of bacteria in tissues such as the genital tract. Our findings suggest that if they have a pathogenic role it is probably minor; however, we did encounter one patient whose treatment was classified as a failure in whom *E. coli* was sensitive to gentamicin but the infecting enterococci were resistant to both drugs.

Two (5%) of the 43 patients in our study had bacteremia, and in both instances it was due to group B β-hemolytic streptococci. Sweet and Ledger[12] documented an 8% frequency of bacteremia, which they correlated with the severity of illness; our experience in this regard was similar.

Although the two treatment regimens used in this study gave satisfactory results, there is clearly room for improvement. We are uncertain about the optimum duration of treatment, although some authors have recommended 4 to 5 days after signs of infection have resolved. In most instances these signs subside within 1 to 3 days; therefore, the timing of antibiotic therapy often corresponds with the duration of stay in hospital. In this population of patients it is appropriate to attempt to shorten the duration of antimicrobial therapy as much as is compatible with the safety of both patient and infant. This is particularly important for mothers who are anxious to breast-feed. We advise against breast-feeding by women who are receiving antibiotics that may be secreted in breast milk, although we do not know of any evidence that such passive antibiotic administration to the baby is harmful in terms of sensitization or modification of bacterial colonization.

A rigidly defined regimen of antimicrobial therapy is undesirable in this group of patients. However, in the early phase of illness empirical antimicrobial therapy is essential pending bacteriologic evaluation. Our findings suggest that a more effective regimen than ampicillin or clindamycin and gentamicin is required.

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