Optimizing Treatment of Intra-amniotic Infection and Early-Onset Postpartum Endometritis: Advantages of Single-Agent Therapy

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Abstract

Introduction: Intra-amniotic infection (IAI) and early-onset postpartum endometritis (PPE) require prompt antibiotic treatment and are generally treated by either of two regimens. A complicated multi-agent regimen is most commonly used, despite a lack of clear evidence that it produces better outcomes than a simpler single-agent regimen.

Objective: We compared treatment outcomes between a multi-agent regimen of ampicillin, gentamicin, and clindamycin versus a single-agent regimen of ampicillin/sulbactam for IAI and early-onset PPE.

Methods: We conducted an observational retrospective cohort study by collecting data from the records of all patients at Denver Health Medical Center treated for IAI or PPE during two 6-month periods: a baseline period during which a regimen of ampicillin, gentamicin, and clindamycin was used and a subsequent period when ampicillin/sulbactam was used. Primary outcomes were prolonged antibiotic treatment and readmission for endometritis or wound cellulitis.

Results: Of potential study participants, 323 women met inclusion criteria; 179 were treated with the multi-agent regimen and 144 were treated with the single-agent regimen. The groups were statistically similar for demographic and intrapartum characteristics, except for a lower rate of premature rupture of membranes in the single-agent treatment group. Twelve patients required prolonged treatment, and 2 were readmitted; these subgroups were combined for statistical analyses. The primary outcomes were significantly associated with cesarean delivery and blood loss >500 mL for vaginal deliveries and >1000 mL for cesarean deliveries; however, there was no significant difference in the incidence of the primary outcomes between the 2 treatment groups when adjusted for these variables. Treatment with ampicillin/sulbactam resulted in fewer antibiotic doses administered to patients with an uncomplicated treatment course.

Conclusion: Ampicillin/sulbactam treatment of IAI and early-onset PPE reduces the number of antibiotic doses administered and results in patient outcomes similar to those for the standard multi-agent therapy of ampicillin, gentamicin, and clindamycin.

Introduction

Intra-amniotic infection (IAI) and early-onset postpartum endometritis (PPE) are common infections during the peripartum period. Clinically diagnosed infection is estimated to occur in 1% to 2% of full-term deliveries and in up to 10% of preterm deliveries[1]; the rates are increased by premature rupture of membranes and cesarean delivery.[2] These polymicrobial infections require broad coverage for gram-positive, gram-negative, and anaerobic bacteria; added anaerobic coverage is beneficial when delivery is cesarean. The most commonly recommended antibiotic treatment regimen employs a combination of ampicillin, gentamicin, and clindamycin for patients not allergic to penicillin; the antibiotics used and the length of treatment vary with the route of delivery. Although the need for prompt antibiotic therapy is well proven,[3] there is no clear evidence indicating that this complicated regimen is superior to others.[4]

Denver Health Medical Center (DHMC) is the safety-net hospital for the city and county of Denver, CO. The staff physicians are exclusively employed by DHMC, and all physicians have academic appointments at the University of Colorado School of Medicine. Like many other institutions, DHMC had long used the multi-agent antibiotic regimen summarized in Figure 1. Although effective, these treatment regimens are confusing and difficult to manage. DHMC has been engaged in lean management strategies[5] since 2005 to eliminate waste from operational and health care processes while maintaining quality and safety. These cumbersome treatment algorithms were seen as an opportunity to apply the lean approach to a patient-care process.

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Several studies have been published that evaluate single-agent antibiotic regimens for the treatment of IAI and PPE.[6,7] In August 2009, DHMC adopted the treatment regimen summarized in Figure 2 for IAI and early-onset PPE for all patients not allergic to penicillin, regardless of delivery method (vaginal vs cesarean) and regardless of time of onset of IAI or PPE. Treatment involves intravenous administration of ampicillin/sulbactam until the patient has been afebrile for 24 hours. Additionally, antibiotic therapy is expanded only if the patient remains febrile beyond 48 hours of antibiotic therapy. To ensure that treatment efficacy was not compromised, we compared maternal outcomes from the 6-month period after the protocol change with those of a 6-month baseline period.

Methods

After obtaining approval from the Colorado Multiple Institutional Review Board, we performed a retrospective review. Using pharmacy records of medication dispensation, we identified all patients who were treated with either gentamicin or ampicillin/sulbactam while admitted to the labor and delivery unit or the postpartum unit at DHMC during two 6-month periods: 1) October 1, 2008, through March 31, 2009, and 2) August 1, 2009, through January 31, 2010. During period 1, the standard, multi-antibiotic regimen of ampicillin, gentamicin, and clindamycin was used to treat patients without penicillin allergies who had IAI and PPE while at DHMC; during period 2, a single-agent regimen of ampicillin/sulbactam was used. The dose amounts and intervals are provided in Figures 1 and 2.

The permanent medical records of all of these patients were reviewed by the authors to confirm that they had been treated for IAI or early-onset PPE, what antibiotics were used, and data for multiple parameters, including the patient's age, patient's ethnicity, infant's gestational age at delivery, route of delivery, maternal estimated blood loss ([EBL] >500 mL for vaginal deliveries; >1000 mL for cesarean deliveries), type of labor onset (spontaneous versus induced), antibiotic treatment received and length of treatment for IAI and PPE, use of prophylaxis for group B *Streptococcus*, readmission to the hospital for endometritis or wound cellulitis, history of preexisting diabetes or gestational diabetes during the pregnancy in question, and timing of membrane rupture (at labor onset or premature). The elapsed time in hours from diagnosis and treatment initiation to delivery was collected from the records of patients in whom IAI was diagnosed before delivery. If the patient had a cesarean delivery, we also recorded whether she received antibiotic prophylaxis within one hour of initiation of the surgical incision.

The inpatient records at DHMC are collected from a combination of electronic systems and paper forms that are then transferred into an electronic data repository. The record in the data repository is the patient's

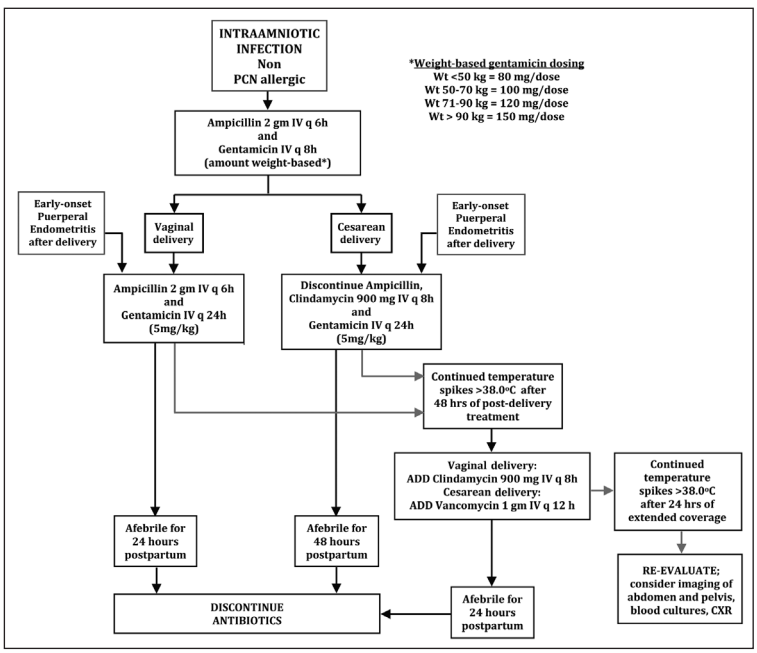

Figure 1. Multi-agent regimen.

CXR = chest x-ray; PCN = penicillin

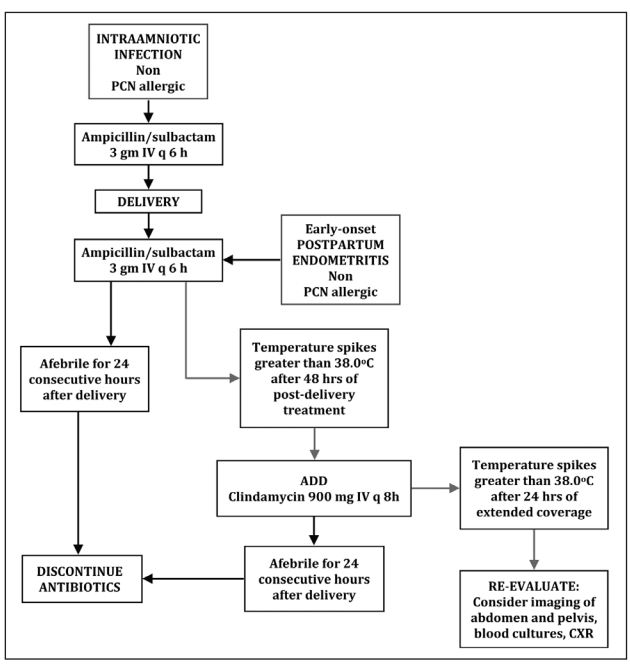

Figure 2. Single-agent regimen.

CXR = chest x-ray; PCN = penicillin

permanent medical record. Patients who had cesarean deliveries during both periods routinely received a single dose of cefotetan within one hour of the surgery start for prophylaxis. A total of 367 records were reviewed; 33 were excluded from analysis because of lack of a diagnosis of IAI or PPE, because of an unknown diagnosis, or because of penicillin allergy, and 11 records were excluded from analysis because the patients were not treated according to either of the regimens.

IAI was diagnosed using the clinical criteria of a temperature of ≥38.0°C plus sustained maternal or fetal tachycardia (maternal rate of >100 beats/min; fetal rate of >160 beats/min), uterine tenderness, maternal leukocytosis (white blood cell count of >15,000 per microliter), or foul-smelling amniotic fluid. PPE was diagnosed by the same clinical criteria, with the addition of foul-smelling lochia and the exclusion of fetal tachycardia and foul-smelling amniotic fluid, occurring within 48 hours of delivery.

The primary outcome variables were an extended course of antibiotic treatment, as defined in the treatment algorithms, or readmission for endometritis or wound cellulitis. The χ^2 test, Fisher's exact test, and Student's *t*-test were used to compare proportional data, and multiple logistic regression was used to identify potential confounding effects of the intrapartum explanatory variables. The statistical software Minitab (version 16.1.1; State College, PA, USA) was used for the analysis.

Results

During the 2008–2009 period, there were 1817 deliveries; during the 2009–2010 period, there were 1867. The proportions of cesarean deliveries during the 2 periods, 19.5% and 19.7%, respectively, were statistically equivalent (χ^2; p = 0.89). Of the 323 patients included in the analysis, 179 were treated by the standard multi-agent regimen of ampicillin, gentamicin, and clindamycin, and 144 were treated by the alternate single-agent regimen of ampicillin/sulbactam. Compliance with the multi-agent regimen was 98.3%; compliance with the single-agent regimen was 97.3%. Table 1 shows that there were no significant differences between the two groups of patients with respect to maternal age, Hispanic ethnicity, route of delivery, preterm delivery, blood loss, induction of labor, penicillin prophylaxis for group B *Streptococcus*, or diabetes; however, there were significantly fewer patients treated with the alternate regimen who had rupture of membranes before labor onset (χ^2; p = 0.01).

Because there were only 14 cases of prolonged treatment or readmission, these outcomes were combined for all analyses. Table 2 shows the results of a binary logistic regression of the primary outcome of prolonged treatment or readmission for endometritis or wound cellulitis and the independent variables of delivery route, preterm delivery, induction of labor, premature rupture of membranes, and EBL >500 mL for vaginal deliveries and >1000 mL for cesarean deliveries. Prophylaxis for group B *Streptococcus* and diabetes were excluded because none of the patients with these factors had prolonged treatment or readmission. Prolonged treatment and readmission were associated with cesarean delivery (odds ratio, 12.7; 95% confidence interval, 3.3–49.0). EBL >500/1000 mL approached statistical significance (p = 0.06); however, cesarean delivery was not associated with an EBL >500/1000 mL when compared with patients who had vaginal deliveries (χ^2; p = 0.33).

Table 3 shows the results of comparing the rates of prolonged treatment or readmission by antibiotic regimen. Of the 323 patients included in the analysis, 12 required prolonged treatment and 2 were readmitted. Of the patients who had prolonged antibiotic treatment, 8 were treated with the multi-agent regimen and 4 were treated with the single-agent regimen. The mean number of days of treatment prolongation was 2.9 in the multi-agent treatment group and 2.5 in the single-agent treatment group (Student's *t*-test; p = 0.55). Two of the patients treated with the single-agent regimen were readmitted with late-onset endometritis and wound cellulitis; 1 of them had a 4-day hospital stay, and the other had a 5-day stay. Of interest, neither of these patients received cefotetan prophylaxis at the time of cesarean delivery. None of the patients with prolonged treatment or who were readmitted was admitted to the intensive care unit or had a return to the operating

Table 1. Comparison of group characteristics

Characteristic	Cases included for analysis (n = 323)		p value (χ^2)
	Multi-agent regimen (%)	Single-agent regimen (%)	
Cases included for analysis	178	145	
Mean age of patients (years)	24.0	24.7	0.35[a]
Hispanic ethnicity	143 (80.3)	112 (77.2)	0.5
Cesarean delivery	53 (30.0)	36 (24.8)	0.4
Preterm delivery	18 (10.1)	11 (7.6)	0.45
Induction of labor	47 (26.4)	36 (24.8)	0.7
Premature rupture of membranes	36 (20.2)	12 (8.3)	<0.00
Diabetes (preexisting or gestational)	10 (5.6)	9 (6.2)	0.8
Estimated blood loss >500 mL (vaginal delivery) or >1000 mL (cesarean delivery)	30 (16.9)	28 (19.3)	0.53
Received penicillin for group B *Streptococcus* prophylaxis	19 (10.7)	16 (11.0)	0.89

[a] Student's *t*-test.

Table 2. Binary logistic regression of independent variables associated with prolonged treatment or readmission

All cases of intra-amniotic infection and postpartum endometritis (n = 323)	Prolonged treatment or readmission			
	Absent[a] (n = 309; 94.7%)	Present (n = 14; 5.3%)	p value	Odds ratio (95% confidence interval)
Cesarean delivery	78 (25.2)	11 (78.6)	<0.00	12.7 (3.3–49.0)
Preterm delivery	28 (9.1)	1 (7.1)	0.76	0.7 (.08–6.3)
Induction of labor	78 (25.2)	5 (35.7)	0.53	0.7 (0.2–2.2)
Premature rupture of membranes	45 (14.6)	3 (21.4)	0.85	0.9 (0.3–3.0)
Estimated blood loss >500 mL (vaginal delivery) or >1000 mL (cesarean delivery)	53 (17.2)	5 (35.7)	0.06	3.5 (1.0–12.3)

[a] Reference category.

Table 3. Binary logistic regression of rates for prolonged treatment or readmission by antibiotic regimen

Group of patients	Multi-agent regimen[a] (%)	Single-agent regimen (%)	p value	Adjusted odds ratio (95% confidence interval)
All patients with IAI and PPE (n = 323)	8/178 (4.5)	6/145 (4.1)	0.86	0.9[b] (0.3–3.0)
Patients with IAI only (n = 223)	6/120 (5.0)	3/103 (2.9)	0.22	0.33[c] (0.1–1.9)
All patients with IAI and PPE (n = 89)	6/53 (11.3)	5/36 (13.9)	0.64	0.67[d] (0.1–3.6)

[a] Reference category.
[b] Adjusted for cesarean delivery, prematurity, induction, PROM, and EBL >500 mL (vaginal) or >1000 mL (cesarean delivery).
[c] Adjusted for cesarean delivery, diagnosis-to-delivery interval, and EBL >500 mL (vaginal delivery) or >1000 mL (cesarean delivery).
[d] Adjusted for prematurity, induction, PROM, cesarean antibiotic prophylaxis, and EBL >500 mL (vaginal delivery) or >1000 mL (cesarean delivery).
EBL = estimated blood loss; IAI = intra-amniotic infection; PPE = postpartum endometritis; PROM = premature rupture of membranes

room. There was no significant difference in the rates of these outcomes between the 2 treatment groups when compared directly (4.5% and 4.1%, respectively; $p = 0.4$, χ^2) or when adjusted for cesarean delivery and blood loss >500/1000 mL.

Of the 323 patients in the analysis, 220 had IAI diagnosed before delivery. The mean number of hours elapsed between diagnosis and start of treatment (antibiotic treatment was uniformly initiated within 1 hour of the time of diagnosis) was 3.5 in the multi-agent treatment group and 3.0 in the single-agent treatment group, not a statistically significant difference (Student's *t*-test; $p = 0.21$). IAI was significantly associated with cesarean delivery ($p < 0.00$) and blood loss >500/1000 mL ($p = 0.02$). Table 3 shows that patients who received the single-agent treatment were less likely to have required prolonged treatment or readmission, but the difference was not statistically significant when adjusted for cesarean delivery, time elapsed from diagnosis to delivery, and EBL ($p = 0.22$).

For the 89 patients who had cesarean deliveries, Table 3 shows that there was no significant difference in the rates of prolonged treatment or readmission by antibiotic treatment regimen when adjusted for prematurity, induction of labor, premature rupture of membrane, antibiotic prophylaxis for cesarean delivery, and blood loss.

Discussion

The prevalence of IAI is as high as 10.5% among laboring women[4]; during the 12-month period of analysis of cases for this study, approximately 9% of the patients who gave birth at DHMC were treated for clinical IAI or endometritis within 48 hours of delivery. The antibiotic combination of ampicillin and gentamicin in laboring patients and after birth in those who have vaginal delivery, with substitution of clindamycin for ampicillin after birth for patients who have cesarean deliveries, is consistently recommended as the treatment of choice, largely on the basis of clinical consensus and extensive study over many years. However, extended-spectrum cephalosporins and penicillins and, more recently, carbapenems have also been shown to be effective single-agent treatments.[2,8] Studies comparing the effectiveness of the single-agent regimens to the standard, multidrug regimen of ampicillin-gentamicin-clindamycin did not show superiority of the single-agent treatments as these medications became available from 1980 to 2000. Because the cost of these newer medications was greater during that period, owing to patent protection, there was no compelling reason to consider routine use of these regimens over the standard treatment. A review published in 2009 in the Cochrane Library concluded that no recommendations could be made with respect to the

most appropriate antibiotic regimen for the treatment of IAI and PPE.[9] Cost was not considered in that analysis.

The obstetrical clinicians at DHMC considered length of treatment, the number of doses of medication administered, and complexity of the treatment algorithm to be important considerations with respect to IAI and early-onset PPE. Inpatient medication-administration error rates are reported to be between 2.4 and 11.1 per 100 doses, with up to 7.5% judged as serious.[10] Minimizing the number of doses per treatment regimen decreases medication-error exposure in addition to saving the direct costs of the drugs and saving pharmacy and nursing time. Ampicillin/sulbactam, originally released under the brand name Unasyn, has been a low-cost alternative since the loss of patent protection in 1999. During the two 6-month periods analyzed, more than 96% of the patients who were treated for IAI and early-onset PPE had uncomplicated treatment courses. Although patients with IAI who had vaginal deliveries were treated for 24 hours after delivery under both regimens, the single-agent treatment group received 3 fewer antibiotic doses than the multi-agent group did. For patients who had cesarean deliveries, the length of treatment after delivery was shortened by 24 hours using the single-agent regimen; 8 post-delivery antibiotic doses were eliminated from the treatment course in each uncomplicated episode.

Minimizing the number of doses per treatment regimen decreases medication-error exposure in addition to saving the direct costs of the drugs and saving pharmacy and nursing time.

Our observational retrospective cohort study has several limitations. The diagnoses of IAI and PPE are made by observation of clinical signs and symptoms that are nonspecific, which can result in variation in interpretation from one clinician to the next. Additionally, these two cohorts had their conditions diagnosed and were treated during different periods, so there could be a greater likelihood of inconsistency in making the diagnosis. The Department of Obstetrics physicians, who are all exclusive employees of DHMC, collectively research and create diagnostic and treatment guidelines for common conditions; deviation from the guidelines is unusual. During these two periods, the diagnostic criteria for IAI and PPE did not change, and there was no significant difference in the rate at which the diagnoses were made.

The purpose of our study was to determine whether there was any loss of treatment efficacy by switching to an alternate antibiotic regimen. With a sample size of 145 and a baseline rate of prolonged treatment or readmission of 4.5% for multi-agent treatment, our study had a power of 0.77 to detect a doubling of the rate to 9% at the level of $\alpha = 0.05$. We did not demonstrate a statistically significant difference in the incidence of the primary outcome of prolonged treatment or readmission; however, the sample size limits the reliability of our study to detect a change in the rate to <9%. Neonatal outcomes were not reviewed.

Conclusion

The results of our study support the use of a single-agent antibiotic, specifically ampicillin/sulbactam, for the treatment of patients without penicillin allergy who have IAI and early-onset PPE. The single-agent treatment algorithm is less complex and results in fewer antibiotic doses administered without a loss of treatment efficacy when compared with the traditional multi-agent regimen. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Acknowledgment

Katharine O'Moore-Klopf, ELS, of KOK Edit provided editorial assistance.

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