The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 199

(Replaces Practice Bulletin Number 120, June 2011)

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Use of Prophylactic Antibiotics in Labor and Delivery

The use of antibiotics to prevent infections during the antepartum, intrapartum, and postpartum periods is different than the use of antibiotics to treat established infections. For many years, the use of prophylactic antibiotics was thought to have few adverse consequences. Concerns about the emergence of resistant strains of common bacteria, in addition to the emergence of strains with increased virulence, have resulted in increased scrutiny of the use of antibiotics, particularly in the hospital setting. Awareness of the potential adverse effects of resistant bacterial infections on neonates has been growing. Attention has been focused on the effect of mode of delivery or early antibiotic exposure on the neonatal oral and gut microbiome, which is essential for immune development. Finally, cost is a consideration in the use and choice of prophylactic agents. The purpose of this Practice Bulletin is to present a review of clinical situations in which prophylactic antibiotics are frequently prescribed and to weigh the evidence that supports the use of antibiotics in these scenarios. This Practice Bulletin is updated to reflect a limited change to clarify and provide additional information on recommendations from recent consensus guidelines for antimicrobial prophylaxis in surgery and the prevention of surgical site infection. The following practices related to cesarean delivery include preoperative skin and vaginal cleansing, weight-based dosage for cefazolin antibiotic prophylaxis, the addition of adjunctive azithromycin antibiotic prophylaxis, and antibiotic selection and dosage for women with a penicillin allergy.

Background

The goal of antibiotic prophylaxis is to prevent infection, not to cure or treat disease. In contrast to the therapeutic use of antibiotics, prophylaxis must be administered before the potential exposure, and usually for a short duration (less than 24 hours). The goal of prophylactic antibiotic use is to have therapeutic tissue levels at the time microbial contamination might occur. Delaying administration by even a few hours reduces or eliminates the benefit of prophylaxis. Ideally, the agent of choice should have a low incidence of adverse effects and be long acting, inexpensive, and narrowly focused on the likely bacterial pathogens, which are usually endogenous flora.

Resistance Risks of Prophylactic Antibiotics

The Centers for Disease Control and Prevention report that 20–50% of all prescribed antibiotics in acute care hospitals in the United States are inappropriate (1). Inappropriate antibiotic use contributes to antibiotic resistance and increased morbidity. In response to these concerns, the Joint Commission developed an antimicrobial stewardship standard for hospitals in January 2017 (2). An antimicrobial stewardship program is designed to promote appropriate use of antibiotics, improve infection cure rates, reduce antibiotic resistance, and decrease the spread of multidrug resistant organisms. Although the risks of inappropriate antibiotic use may be difficult to

recognize in an individual patient, the broader effect of the increasing use of antibiotics can be seen at the hospital level. Antimicrobial prophylaxis has been shown to result in marked changes in an individual's skin flora, with increases in resistant flora seen postoperatively (3). This appears to be the result of selection of resistant endogenous flora by prophylactic antibiotics, as well as the nosocomial acquisition of resistant microorganisms.

Awareness of the potential adverse effects of resistant bacterial infections on neonates has been increasing. Changes have been reported in resistance patterns of isolated strains of *Escherichia coli* in newborns, particularly after maternal antibiotic administration (4–9). The increases in E coli sepsis and the increasing resistance to ampicillin are primarily confined to the preterm population and low-birth-weight population, although an effect on term infants has been suggested as well (10, 11). A comparison of very-low-birth-weight neonates (less than 1,500 g) born between 1998 and 2000 with neonates born between 1991 and 1993 found an important reduction in early-onset neonatal sepsis from group B streptococci (GBS), but an increase in sepsis caused by E coli (12). Sepsis in very-low-birth-weight neonates with ampicillin-resistant E coli is more likely to be fatal than infection with susceptible strains (8). In addition to resistant E coli, some studies show that up to 30% of GBS isolates are resistant to erythromycin and clindamycin. These results have led to significant changes in intrapartum protocols designed to prevent invasive neonatal GBS disease (13–16).

In the past, antibiotic resistance has been countered by the development of new classes of drugs or modifications of older drugs. However, it seems increasingly unlikely that the pharmaceutical industry will be able to keep pace with the rapid emergence of resistant organisms (17). In the past two decades, for example, increasing difficulties have been encountered in treating multidrug-resistant tuberculosis as well as resistant strains of *Staphylococcus aureus*, enterococci, and *Streptococcus pneumoniae* (18). Furthermore, the cost of methicillin-resistant *Staphylococcus aureus* (MRSA) infection treatment among obstetric patients has been estimated to be more than $8 million annually in the United States alone (19).

Antibiotic Allergy and Anaphylaxis Risks

Other risks of antibiotic administration include allergic reactions or anaphylaxis, although the true incidences of these risks are unclear. One early study reported that approximately 25% of all patients that required antimicrobial therapy in the hospital reported an allergy to at least one antibiotic, typically penicillin, and only 4% of those patients had documentation as to the specific type of allergic reaction (20). Even with widespread electronic medical record use, the specific allergic reaction is not always documented, making it difficult to distinguish between a true allergy and an adverse effect of the medication (21). Nevertheless, a severe allergic reaction (eg, anaphylaxis) to penicillin is estimated to occur in 1 in 2,500–25,000 patients, with less severe reactions occurring in approximately 10% of patients (10). It has been estimated that approximately 5% of patients who received an antibiotic in the hospital will have a severe adverse reaction (22). Furthermore, up to 10% of patients with a history of a penicillin allergy may react if given a cephalosporin (23). Skin reactions (urticaria, rash, pruritus) to cephalosporins occur in 1–3% of patients; however, the risk of anaphylaxis is thought to be much lower (0.001–0.1%) (23). A case of anaphylaxis to penicillin after administration for GBS prophylaxis has been reported, and there are reports of exfoliative dermatitis and severe immune hemolytic anemia associated with cephalosporin therapy (23–25). Although these instances are uncommon, antibiotic use should be limited to the specific indications as outlined and customized as needed in cases of allergy.

Penicillin allergy skin testing can be considered in evaluation of patients with a history of an allergy to penicillin. Skin testing, even after delivery, could decrease the morbidity and economic costs associated with treating these patients with costly alternative antibiotics that also may result in adverse consequences (26).

Pharmacokinetics of Antibiotics

It has long been assumed that the pharmacokinetics of antibiotics differ between pregnant and nonpregnant patients as a result of the physiologic changes of pregnancy. The increase in the glomerular filtration rate that begins early in the first trimester during pregnancy may decrease drug half-lives resulting in lower peak serum levels in pregnant women. Because of the increased plasma volume in pregnancy, the volume of distribution is greater and the concentration of plasma proteins is lower than in the nonpregnant state, which also potentially leads to lower plasma and serum levels of antibiotics. Hormone-mediated increases in binding proteins may result in changes in the distribution of drugs, whereas decreases in gastric emptying time and changes in gastric acidity may change the oral absorption of drugs. Overall, these considerations are believed to result in a reduction in the amount of the drug available to a pregnant woman and, potentially, a need for increased antibiotic dosages during pregnancy.

When therapeutic levels of antibiotics in the amniotic cavity are desired, agents known to have efficient transplacental transfer should be used. A clinical example is maternal intrapartum prophylaxis for GBS. Antibiotics that are known to reach fetal concentrations of 30–90% of maternal serum in the second trimester and beyond include ampicillin, cephalothin, clindamycin, vancomycin, azithromycin, and the aminoglycosides (27–30).

Increased doses of prophylactic antibiotics have been recommended for an obese patient (weight greater than 80 kg [175 lb] or body mass index [BMI, calculated as weight in kilograms divided by height in meters squared] greater than 30) (31, 32). Cephalosporins, which are commonly used prophylactic antibiotics, have increased volume of distribution and drug clearance in obese patients (33–35). Initial recommendations for increased doses of cefazolin from 1 g to 2 g were based on the bariatric surgery literature. These studies had shown that a single preoperative 2-g dose of cefazolin achieved intraoperative serum and tissue levels comparable with those seen in nonobese patients given a 1-g dose (34, 36). Although a 1-g dose can be considered in patients weighing 80 kg or less, for simplification, some hospitals have standardized a 2-g cefazolin dose for all adults (31).

Current consensus guidelines have further increased the dose to 3 g for antibiotic prophylaxis in patients weighing 120 kg or more who are undergoing nonobstetric surgery (31, 32). However, data from the obstetric population are conflicting regarding 2-g versus 3-g cefazolin doses in obese women. Two clinical studies support a 3-g cefazolin dose among obese patients (37, 38), whereas two others do not (39, 40). In one cohort study, obese and extremely obese women (BMI 40 or higher) who were given prophylactic 2-g cefazolin had antibiotic tissue concentrations at the time of skin incision that were less than 4 micrograms/g of tissue, which is the minimally inhibitory concentration (MIC) for Gram-negative rods. A considerable portion of obese and extremely obese women did not achieve MIC of greater than 4 micrograms/g for Gram-negative rods in adipose samples at skin incision (20% and 33%, respectively) or closure (20% and 44%, respectively) (37). However, among trials that randomized obese pregnant women to prophylactic 2-g versus 3-g cefazolin, adipose tissue concentrations did not significantly differ between the two dosages (39, 40). Because of these conflicting outcomes likely due to differences in study design, sampling, and MIC definitions, a population pharmacokinetic analysis was performed using aggregated data from three of these clinical studies (41). This modeling study concluded that a 2-g dose of cefazolin had a high probability of achieving concentrations above the MIC in overweight and obese women. Furthermore, a multicenter retrospective cohort study that compared 2-g versus 3-g cefazolin among 335 obese women weighing more than 300 lbs did not find a reduction in surgical site infections (13.1% in 2-g group versus 13.1% in 3-g group) (42).

Clinical Considerations and Recommendations

▶ ***Are antimicrobial skin and vaginal preparations effective in reducing infections after cesarean delivery?***

Because of the dual source of infectious organisms (ie, skin and vagina) in cesarean deliveries, investigators have explored interventions other than parenteral antibiotics to prevent infections such as antimicrobial skin and vaginal cleansing agents. The Centers for Disease Control and Prevention recommends that preoperative skin cleansing before cesarean delivery with an alcohol-based solution should be performed unless contraindicated (43). A reasonable choice is a chlorhexidine–alcohol skin preparation (31, 32, 44). Additionally, cleansing the vagina with an antiseptic solution immediately before cesarean has been adopted into some practices. A meta-analysis demonstrated that preoperative vaginal cleansing in laboring patients or those with ruptured membranes reduced the risk of endometritis and postoperative fever, but not wound infection (45). The majority of included studies used 10% povidone–iodine on a sponge stick for 30 seconds. Also, a single trial of 0.25% chlorhexidine vaginal wipes before elective cesarean delivery reported reduced infectious morbidity overall, which was largely due to a reduction in endometritis (46). Vaginal cleansing before cesarean delivery in laboring patients and those with ruptured membranes using either povidone–iodine or chlorhexidine gluconate may be considered. Chlorhexidine gluconate solutions with high concentrations of alcohol are contraindicated for surgical preparation of the vagina, but solutions of chlorhexidine gluconate with low concentrations of alcohol (eg, 4%) are safe and effective for off-label use as vaginal surgical preparations and may be used as an alternative to iodine-based preparations in cases of allergy or when preferred by the surgeon.

▶ ***Is antibiotic prophylaxis appropriate for patients undergoing cesarean delivery?***

The single most important risk factor for infection in the postpartum period is cesarean delivery, with rates of postoperative infection significantly higher than would be predicted compared with rates from other surgical procedures (47–49). As with other noninfected surgical cases, antibiotic prophylaxis is recommended for all

cesarean deliveries unless the patient is already receiving an antibiotic regimen with equivalent broad spectrum coverage (eg, for chorioamnionitis), and such prophylaxis should be administered within 60 minutes before the start of the cesarean delivery (31, 43). When this is not possible (eg, need for emergent delivery), prophylaxis should be administered as soon as possible after the incision is made.

A Cochrane review included 95 studies with more than 15,000 participants enrolled in randomized clinical trials to evaluate the effect of prophylactic antibiotics in both emergent and nonemergent cesarean deliveries (50). This review found significant reductions in overall febrile morbidity, wound complications, and endometritis with the use of prophylactic antibiotics. In this analysis, the risk of endometritis after elective cesarean delivery, for example, was reduced by 62% (relative risk [RR], 0.38; 95% CI, 0.24–0.61). All risk reductions remained significant regardless of the type of cesarean delivery (emergent or elective). Additionally, in a secondary analysis of data from more than 9,000 U.S. women enrolled in the Maternal–Fetal Medicine Units Network Cesarean Registry study, there was a significant reduction in postpartum endometritis and wound complications when antibiotic prophylaxis was administered at the time of a term prelabor cesarean delivery. These risk reductions remained significant when the analysis was controlled for patients who had rupture of membranes, but not labor, before their surgery (51).

Timing and Choice of Antibiotic Regimen

Antibiotics that are effective against Gram-positive bacteria, Gram-negative bacteria, and some anaerobic bacteria are used for prophylaxis for cesarean delivery. A variety of antibiotics have been shown to be efficacious for prophylaxis, including cefazolin, cefotetan, cefuroxime, ampicillin, piperacillin, cefoxitin, and ampicillin–sulbactam. One retrospective study of 2,280 nonelective cesarean deliveries reported that cefazolin, a first-generation cephalosporin, and cefoxitin, a second-generation cephalosporin, were equally efficacious in preventing endometritis, with cefazolin costing 80% less than cefoxitin (52). Similarly, a meta-analysis of 27 antibiotic trials confirmed that ß-lactam and cephalosporins had comparable efficacy for cesarean delivery prophylaxis (53).

Single-dose therapy has been shown to be as efficacious as multidose therapy for uncomplicated cesarean deliveries in most studies (54). Single-dose therapy also reduces costs, potential toxicity, and the risk of colonization with resistant organisms. For cesarean delivery prophylaxis, a single dose of a targeted antibiotic, such as a first-generation cephalosporin, is the first-line antibiotic of choice, unless significant drug allergies are present. For women with a history of a significant penicillin or cephalosporin allergy (anaphylaxis, angioedema, respiratory distress, or urticaria), a single-dose combination of clindamycin with an aminoglycoside is a reasonable alternative for cesarean delivery prophylaxis, although data are limited to support this recommendation.

A 1-g intravenous dose of cefazolin as prophylaxis before cesarean delivery may be considered for women weighing 80 kg or less. Considering the low cost and favorable safety profile of cefazolin, current consensus guidelines have suggested that weight-based dosages may be considered acknowledging that outcome studies have not shown a decreased infection morbidity in heavier patients (31, 32). Increasing the dose to 2 g for patients weighing 80 kg or more is recommended; however, the benefit of administering 3 g in obstetric patients weighing 120 kg or more has not yet been established (Table 1). For ease of administration, some institutions uniformly dispense a 2-g cefazolin dose for all adult patients undergoing cesarean delivery.

Extended-spectrum antibiotics, such as azithromycin, have been suggested as alternatives or adjuncts to first-generation cephalosporins for cesarean delivery prophylaxis, administered either before or after umbilical cord clamping. In one review, the benefit of postincision administration of azithromycin appeared to be comparable to preincisional cefazolin (55). A multicenter randomized controlled trial evaluated the benefits of 500 mg of intravenous azithromycin infused over 1 hour in addition to a standard antibiotic prophylaxis regimen in 2,013 women undergoing nonelective cesarean (56). Women who received adjunctive azithromycin had a significant reduction in the primary composite outcome of endometritis, wound infection, or other infections (RR, 0.51; 95% CI, 0.38–0.68, $P<.001$). The number of patients who would need to be treated to prevent one study outcome was 17 (95% CI, 12–30). There was no significant difference in the neonatal composite outcome that included death and serious neonatal complications. Adjunctive azithromycin in cost-effective analyses has been shown to be cost-saving in nonelective (57, 58) and elective cesarean deliveries (57). However, no randomized clinical trials are available for the effect of azithromycin antibiotic prophylaxis on infection morbidity with elective cesarean delivery. Given these findings, the addition of azithromycin, infused over 1 hour, to a standard antibiotic prophylaxis regimen may be considered for women undergoing a nonelective cesarean delivery.

Table 1. Surgical Weight-Adjusted Antibiotic Prophylaxis Regimens

Weight	Antibiotic	Intravenous Regimen
Normal BMI (weight≤80 kg)	Cefazolin or clindamycin plus aminoglycoside*	1 g† 900 mg plus 5 mg/kg‡
Obese (BMI≥30 or weight≥80 kg)	Cefazolin or clindamycin plus aminoglycoside*	2–3 g§ 900 mg plus 5 mg/kg‖

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

*Significant penicillin or cephalosporin allergy (anaphylaxis, angioedema, respiratory distress, or urticaria).

†Expert opinion has advocated that, for simplification, some hospitals have standardized 2-g cefazolin doses for all adult patients.

‡Although U.S. Food and Drug Administration-approved package insert labeling recommends a range of dosage options, expert opinion used the most-often recommended dose.

§Consensus guidelines in nonobstetric patients suggest increasing the dose to 2 g for patients weighing 80 kg or more and 3 g for those weighing 120 kg or more.

‖Dose is based on the patient's actual body weight. If the patient's actual weight is more than 20% above ideal body weight (IBW), the dose can be determined as follows: dose=IBW+0.4 (actual weight−IBW).

Data from Anderson DJ, Podgorny K, Berríos-Torres SI, Bratzler DW, Dellinger EP, Greene L, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol 2014;35:605–27; *and* Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. American Society of Health-System Pharmacists, Infectious Disease Society of America, Surgical Infection Society, Society for Healthcare Epidemiology of America. Am J Health Syst Pharm 2013;70:195–283.

The most appropriate timing for administration of prophylactic antibiotics also has been thoroughly studied. A meta-analysis of three randomized trials, with a combined sample size of 749 participants, supported the use of antibiotic prophylaxis for cesarean delivery administered up to 60 minutes before skin incision rather than after umbilical cord clamping (59). Antibiotic prophylaxis before skin incision was found in this study and a later systematic review to decrease the incidence of postpartum endometritis and total infection morbidity without affecting neonatal outcomes (60). Two subsequent, retrospective cohort studies from large centers evaluated the effect of policy change at these institutions from administering antibiotics after umbilical cord clamping to administering preincisional cesarean prophylaxis to all patients. These two studies reinforced the findings of low rates of surgical site infections and overall maternal infection morbidities with presurgical prophylaxis. No differences in rates of neonatal intensive care unit admission, neonatal sepsis, or suspected sepsis were reported between the treatment groups, although, as with other studies, power calculations were not based on evaluation of these secondary neonatal outcomes (61, 62). In addition, a retrospective case–control study of 1,600 patients who underwent cesarean delivery showed that antibiotic prophylaxis administered more than 1 hour before incision was associated with double the rate of surgical site infections compared with timing within 1 hour of incision (RR, 2.1; CI, 1.2–3.8) (63). For most antibiotics, including cefazolin, prophylaxis should be administered within 1 hour before skin incision. Additionally, patients with lengthy surgical procedures (eg, greater than two drug half-lives of the antibiotic, which is 4 hours for cefazolin and measured from the initiation of the preoperative dose, not from the onset of surgery) or those who experience excessive blood loss (eg, greater than 1,500 mL) should receive an additional intraoperative dose of the same antibiotic given for preincision prophylaxis (31, 32, 44).

The role of postcesarean delivery antibiotic prophylaxis to reduce surgical site infection among obese women is emerging. One single-center, double-blind clinical trial randomized women after cesarean delivery with a standard 2-g cefazolin prophylaxis to a 48-hour course of 500-mg oral cephalexin and 500-mg metronidazole every 8 hours or placebo (64). Surgical site infections were lower among those receiving oral antibiotics (6.4% versus 15.4%; RR, 0.41 [95% CI, 0.22–0.77]). This study was in its final year of data collection when the C/SOAP trial (56) demonstrated a decrease in postcesarean surgical site infection by expanding the preoperative antimicrobial spectrum with azithromycin for cesarean antiinfection prophylaxis. Therefore, it is unclear if the demonstrated benefit of additional oral antibiotics would exceed that of administration of intravenous azithromycin at the time of the

cesarean delivery. In obese individuals who may not have received antibiotic prophylaxis with intravenous azithromycin because of unforeseen circumstances (or the need for infusion over 1 hour), this postoperative oral regimen may be considered. The rate of postoperative surgical site infection in women who received oral antibiotics is similar to the rate of women that receive adjunctive azithromycin (6.4% versus 6.1%, respectively) (56, 64).

▶ *Does colonization with methicillin-resistant* S aureus *affect antibiotic prophylaxis for cesarean delivery?*

The epidemiology of MRSA infections has changed from primarily hospital-acquired infection among ill or immunocompromised patients to infections related to the emergence of more virulent MRSA strains over the past 10 years, which constitutes a major public health problem no longer confined to intensive care units or health care institutions in general (65–68). In one survey, MRSA isolation among patients with culture-confirmed surgical site infection increased from 16% to 21% over a 5-year study period (69). Methicillin-resistant *Staphylococcus aureus* has been associated with serious postpartum infections, particularly after cesarean delivery (70, 71), and surveillance studies have detected MRSA colonization rates of up to 10% in rectovaginal swab specimens and up to 2% of nasal swab specimens in asymptomatic pregnant women at term (72, 73). Despite these increasing concerns, there are currently insufficient data in pregnant patients to warrant or recommend screening all women preoperatively for MRSA colonization status, particularly because most colonized patients will not develop invasive disease.

Although intranasal or topical (skin wash) antimicrobial decolonization protocols have been studied for the prevention of recurrent skin and soft tissue infections among MRSA carriers, the overall efficacy, optimal dosage, and duration for these regimens remain uncertain (74). In the context of skin and soft tissue infections alone, nasal mupirocin has been shown to decrease the prevalence of nasal MRSA colonization, but not to reduce the incidence of first-time skin and soft tissue infections (75). In addition, concerns about high levels of mupirocin resistance have been raised by analysis of MRSA isolates in some community settings (76). Although a preoperative skin preparation using chlorhexidine–alcohol was shown to reduce rates of surgical infections compared with povidone iodine (77), chlorhexidine skin wipes used alone had no effect on lowering skin and soft tissue infections rates among MRSA carriers (78). Finally, a Cochrane review found no benefit from oral antibiotics for eradication of MRSA colonization among patients in the health care setting (79), and oral antibiotics are not currently routinely recommended for the purpose of MRSA decolonization (74).

Any potential benefit of preoperative decolonization protocols for MRSA carriers may be limited in obstetric populations to women who have a planned cesarean delivery and who are known before the delivery to be MRSA colonized (defined as those with a history of MRSA infection or positive culture in the past). Routine screening of obstetric patients for MRSA colonization is not recommended. However, in obstetric patients known to be MRSA colonized, consideration may be given to adding a single dose of vancomycin to the recommended antibiotic prophylaxis regimen for women undergoing cesarean delivery (cefazolin or an alternative for patients with β-lactam allergies). Vancomycin alone does not provide sufficient coverage for cesarean delivery surgical prophylaxis.

▶ *Is antibiotic prophylaxis appropriate for patients with preterm prelabor rupture of membranes?*

For patients with prelabor rupture of membranes (also referred to as premature rupture of membranes) (PROM) at less than 34 0/7 weeks of gestation, antibiotic prophylaxis is indicated to prolong the latency period between membrane rupture and delivery (15, 80) (see Box 1). Numerous trials have evaluated the prophylactic use of intravenous and oral antibiotics to prolong latency and to improve maternal and neonatal outcomes after

Box 1. Recommendations for Use of Antibiotics in Women With Preterm Prelabor Rupture of Membranes or Preterm Labor

For Patients With Preterm Labor With Intact Membranes

- Use intrapartum antibiotics to prevent group B streptococcal perinatal infection.
- Do not use antibiotics to prolong pregnancy.

For Patients With Preterm Prelabor Rupture of Membranes Less than 34 0/7 Weeks of Gestation

- A 2-day course of therapy with a combination of intravenous ampicillin and erythromycin followed by a 5-day course of oral amoxicillin and erythromycin is recommended to prolong pregnancy and decrease short-term neonatal complications.

preterm PROM (81–86). Regardless of the antibiotic prescribed or the duration of treatment, most trials described a statistically significant prolongation of the latency period but generally did not show an improvement in neonatal outcome. However, a Maternal–Fetal Medicine Units Network multicenter trial demonstrated a reduction in neonatal morbidity and mortality with antibiotic prophylaxis, including reductions in respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, and early onset sepsis (85). In this study, neonates of GBS-positive women did not receive the same benefit, which was likely a result of the placebo and treatment groups receiving antepartum and intrapartum ampicillin in addition to the study medications. None of the patients received antenatal corticosteroids.

A meta-analysis concluded that antibiotic prophylaxis after preterm PROM is effective in prolonging pregnancy, reducing maternal infectious complications, and reducing neonatal infection morbidity (86). However, a large multicenter trial from the United Kingdom reported that pregnancy was prolonged by the use of erythromycin, amoxicillin–clavulanic acid, or both, but amoxicillin–clavulanic acid was associated with an increased risk of neonatal necrotizing enterocolitis (87). A review of the current literature does not reveal a consistent pattern of increased risk with broader-spectrum antibiotic therapy, and one retrospective review of the use of amoxicillin–clavulanic acid did not demonstrate an association with necrotizing enterocolitis (88). However, amoxicillin–clavulanic acid is not recommended given the possible increased risk of necrotizing enterocolitis (80).

The American College of Obstetricians and Gynecologists and the Society of Obstetricians and Gynaecologists of Canada recommend the use of prophylactic antibiotics for preterm PROM (less than 34 0/7 weeks of gestation) when fetal lung maturity is not documented and delivery is not imminent, with options including a regimen of amoxicillin and erythromycin for a total of 7 days (80, 89). Azithromycin has been substituted in situations for which erythromycin is not available (90). Substitution of azithromycin for erythromycin did not affect latency or other maternal or fetal outcomes in one retrospective cohort study, but dose and route of administration were not specified (91). Several studies have attempted to determine whether a duration shorter than 7 days of antibiotic therapy could be adequate after preterm PROM, but the studies have been of inadequate size and power to demonstrate equivalent effectiveness in reducing infant morbidity (92, 93).

Revised guidelines from the Centers for Disease Control and Prevention recommend women with preterm PROM to be screened for GBS on admission. If the patient completes the full 7-day course of latency antibiotics and remains without evidence of infection or labor, intrapartum GBS prophylaxis should then be managed by the results of the baseline GBS test at the time of preterm PROM. If the patient remains pregnant 5 or more weeks after a negative baseline GBS test, then GBS screening should be repeated (15, 16); a positive baseline test does not have to be repeated and the patient should receive GBS prophylaxis.

▶ *Is antibiotic prophylaxis appropriate for preterm labor?*

Antibiotic use intended only for pregnancy prolongation in women with preterm labor with intact membranes does not have short-term neonatal benefits and may be associated with long-term harm. Thus, antibiotic prophylaxis should not be used for pregnancy prolongation in women with preterm labor and intact membranes (94). This recommendation is distinct from recommendations for antibiotic use for preterm PROM and GBS carrier status (8, 15, 95).

In cases of preterm labor with intact membranes, intravenous GBS prophylaxis should be administered until GBS test results are available unless the patient has had a negative GBS test result within the preceding 5 weeks. If the GBS test result obtained at the time the patient was admitted is positive but true labor does not ensue, the GBS prophylaxis should be discontinued and restarted at the onset of true labor (15).

A multicenter, randomized clinical trial provided 7-year follow-up of a large group of patients receiving antibiotics (placebo versus oral erythromycin, amoxicillin–clavulanate, or both) for preterm labor with intact membranes. From this trial, 3,196 children (71% of those enrolled) had outcome information available (96). Despite being comparable in acute morbidities and mortality, the study groups were significantly different in terms of long-term follow-up neurologic morbidity. Infants exposed prenatally to erythromycin, had more functional impairment (42.3% versus 38.3%) and mild functional impairment (23.9% versus 21.3%) compared with those who had not received erythromycin. These data reinforce the lack of benefit and the potential harm in using antibiotic prophylaxis for preterm labor with intact membranes, in contrast to its use with preterm PROM. However, further follow-up of these infants at 11 years of age showed no differences in educational test scores and special needs (97).

▶ *Is antibiotic prophylaxis appropriate for prevention of bacterial endocarditis at the time of delivery?*

Infective endocarditis prophylaxis is not recommended for women with acquired or congenital structural heart disease for either vaginal or cesarean delivery in the absence of infection, except possibly for the small subset of patients at highest potential risk of adverse cardiac outcomes (98, 99). Joint statements from the American Heart Association and the American College of Cardiology recommend this approach for three main reasons: 1) most cases of endocarditis are not attributable to an invasive procedure (whether dental, gastrointestinal, or genitourinary), but rather are the result of randomly occurring bacteremia from routine daily activities; 2) prophylaxis may prevent only a small number of cases of infective endocarditis in women undergoing genitourinary procedures; and 3) the risk of antibiotic-associated adverse events exceeds the benefit, if any, from prophylactic antibiotic therapy (98, 100).

Only cardiac conditions associated with the highest risk of adverse outcomes from endocarditis are appropriate for infective endocarditis prophylaxis, and this is primarily for patients undergoing dental procedures that involve manipulation of gingival tissue or the periapical region of teeth, or perforation of the oral mucosa (see Box 2). However, because of the potential for significant morbidity and mortality, based on expert opinion and a limited retrospective study of women with congenital heart disease (101), the American Heart Association and the American College of Cardiology recommend that the use of prophylactic antibiotic therapy be considered for vaginal delivery in patients with the highest risk of adverse outcomes from endocarditis. Those at highest risk are women with cyanotic cardiac disease, or prosthetic valves, or both (99). Mitral valve prolapse is not considered a lesion that ever needs infective endocarditis prophylaxis. For those not already receiving intrapartum antibiotic therapy for another indication that would also provide coverage against endocarditis, antibiotic regimens for endocarditis prophylaxis (Table 2) can be administered as close to 30–60 minutes before anticipated time of delivery as is feasible.

In patients with one of these high-risk conditions and who have an established infection that could result in bacteremia, such as chorioamnionitis or pyelonephritis, the underlying infection should be treated to prevent infection or sepsis, but specific additional endocarditis prophylaxis is not recommended (100). In such cases, the regimen being used to treat the established infection will almost uniformly already contain an agent that is recommended as a single-dose for prophylaxis with dental procedures (ampicillin or amoxicillin, cefazolin, or ceftriaxone, clindamycin, or azithromycin) (see Table 2). Multiple-dose combination regimens are no longer indicated or recommended for prophylaxis, even in the context of invasive dental procedures.

Box 2. Cardiac Conditions With High Risk of Endocarditis in the Presence of Bacteremia

Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk of adverse outcomes from infective endocarditis*:

- Patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair
- Patients with previous infective endocarditis
- Patients with CHD
  - Unrepaired cyanotic CHD, including palliative shunts and conduits
  - Completely repaired congenital heart defect repaired with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure.
  - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (both of which inhibit endothelialization)
- Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve.

Abbreviation: CHD, congenital heart disease.

*Prophylaxis against infective endocarditis is not recommended for nondental procedures in the absence of active infection.

Data from Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin VH, Sundt TM III, Thompson A. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017;135:e1159–95.

▶ *Is antibiotic prophylaxis appropriate for patients undergoing repair of third-degree lacerations or fourth-degree lacerations?*

The use of prophylactic antibiotics in the setting of severe perineal trauma or obstetric anal sphincter injuries (OASIS) has not been extensively studied. A retrospective cohort investigation demonstrated a reduction in wound complications among women who received intrapartum antibiotics before delivery for GBS or

Table 2. Infective Endocarditis Antibiotic Prophylaxis Regimens for High-Risk Women

Treatment	Antibiotic	Regimen (Preferably Treatment Antibiotic 30–60 min Before Procedure)
Intravenous therapy	Ampicillin or cefazolin or ceftriaxone*	2 g intravenously 1 g intravenously
Allergic to penicillin or ampicillin*	Cefazolin or ceftriaxone* or clindamycin	1 g intravenously* 600 mg intravenously
Oral	Amoxicillin	2 g
Allergic to penicillin or ampicillin†	Cephalexin*	2 g
	Clindamycin	600 mg
	Azithromycin	500 mg

*Cephalosporins should not be used in patients with a significant sensitivity to penicillins.

†This regimen does not cover enterococcus. Vancomycin can be used if enterococcus is of concern.

Data from Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group [published erratum appears in Circulation 2007;116:e376–7]. Circulation 2007;116:1736–54. Available at: http://circ.ahajournals.org/content/116/15/1736.long. Retrieved April 5, 2018.

chorioamnionitis (adjusted odds ratio, 0.29: 95% CI, 0.14–0.59) (102). A subsequent prospective cohort investigation from the same institution demonstrated a reduction in wound complications (adjusted odds ratio, 0.50; 95% CI, 0.27–0.94) with intrapartum antibiotics given for any obstetric reason; however, there was no difference in wound complications among women who received antibiotics specifically for OASIS (103). A single randomized trial suggested that a single dose of a second-generation cephalosporin (cefotetan or cefoxitin), or clindamycin if the patient was penicillin allergic, was protective against perineal wound complications (8.2% in the treatment group at 2 weeks, compared with 24.1% in the control group; RR, 0.34; 95% CI, 0.12–0.96, $P=.04$). Although this study had a follow-up loss rate of 27%, and its findings have not been replicated (104), a single dose of antibiotic at the time of repair is reasonable in the setting of OASIS. Further research is needed to determine whether severe perineal lacerations warrant routine postpartum antibiotics to prevent complications.

▶ *Is antibiotic prophylaxis appropriate for patients undergoing cervical cerclage?*

Because the rate of complications (including infection complications) after history-indicated cerclage (when performed before any evidence of cervical dilatation or shortening) is low (1–5%), a study with a sufficiently large sample size to determine whether prophylactic antibiotic therapy is of benefit would be extremely difficult to implement (105). Evidence is insufficient to recommend antibiotic prophylaxis for history-, ultrasonography-, or examination-indicated cervical cerclage.

Cerclage performed later in pregnancy, and when cervical dilatation and effacement are present, has a high rate of complications, including chorioamnionitis and rupture of membranes (105, 106). In addition, the risk of preexisting, often subclinical, chorioamnionitis as a cause of the cervical insufficiency is significant, averaging approximately 33% (105, 107). In one trial, median gestational latency did not differ between intervention and control among a group of 53 women randomized to indomethacin and antibiotics or placebo (108); however, when analyzed categorically, there was a significant increase in the frequency of latency greater than 28 days among women who received the intervention (92.3% versus 62.5%, $P=.01$). Neither perinatal survival or the composite adverse neonatal outcome differed between groups. Other randomized trials of cerclage in high-risk and low-risk individuals with cervical shortening have not uniformly included antibiotic prophylaxis as part of their protocols and, therefore, the current evidence is insufficient to recommend for or against antibiotic prophylaxis for either history-, ultrasonography-, or examination-indicated cerclage (109, 110). If prophylaxis

is used in such a situation, it should be guided by the general principles previously outlined, particularly a focused coverage spectrum and short duration.

Similarly, consistent data are lacking regarding the use of antibiotic prophylaxis for abdominal cerclage. Because this procedure is performed with laparotomy or laparoscopy, routine prophylaxis would not be indicated in accordance with recommendations for other gynecologic surgical procedures performed with these approaches (44).

▶ ***Is antibiotic prophylaxis appropriate for patients undergoing other obstetric procedures (ie, manual removal of the placenta, intrauterine balloon catheters, or dilatation and curettage)?***

Several studies document the increased risk of postpartum endometritis after manual removal of the placenta during cesarean delivery, even in the presence of antibiotic prophylaxis (111–113). Although existing data do not support this practice, it is common to administer prophylactic antibiotics to patients who give birth vaginally and in whom a manual removal of the placenta has been performed (114). Although antimicrobial prophylaxis is recommended for women undergoing uterine evacuation for induced abortion or early pregnancy loss (44), there are no data to recommend for or against prophylactic antibiotics for postpartum dilatation and curettage or placement of indwelling intrauterine balloon catheters in the clinical situation of retained placenta or postpartum hemorrhage.

Summary of Recommendations and Conclusions

The following recommendations and conclusions are based on good and consistent scientific evidence (Level A):

- ▶ Antibiotic prophylaxis is recommended for all cesarean deliveries unless the patient is already receiving an antibiotic regimen with equivalent broad-spectrum coverage (eg, for chorioamnionitis), and such prophylaxis should be administered within 60 minutes before the start of the cesarean delivery.
- ▶ For cesarean delivery prophylaxis, a single dose of a targeted antibiotic, such as a first-generation cephalosporin, is the first-line antibiotic of choice, unless significant drug allergies are present.
- ▶ The addition of azithromycin, infused over 1 hour, to a standard antibiotic prophylaxis regimen may be considered for women undergoing a nonelective cesarean delivery.
- ▶ Vaginal cleansing before cesarean delivery in laboring patients and those with ruptured membranes using either povidone–iodine or chlorhexidine gluconate may be considered. Chlorhexidine gluconate solutions with high concentrations of alcohol are contraindicated for surgical preparation of the vagina, but solutions of chlorhexidine gluconate with low concentrations of alcohol (eg, 4%) are safe and effective for off-label use as vaginal surgical preparations and may be used as an alternative to iodine-based preparations in cases of allergy or when preferred by the surgeon.
- ▶ Preoperative skin cleansing before cesarean delivery with an alcohol-based solution should be performed unless contraindicated. A reasonable choice is a chlorhexidine–alcohol skin preparation.
- ▶ For patients with prelabor rupture of membranes (PROM) at less than 34 0/7 weeks of gestation, antibiotic prophylaxis is indicated to prolong the latency period between membrane rupture and delivery.
- ▶ Antibiotic prophylaxis should not be used for pregnancy prolongation in women with preterm labor and intact membranes. This recommendation is distinct from recommendations for antibiotic use for preterm PROM and GBS carrier status.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- ▶ For women with a history of a significant penicillin or cephalosporin allergy (anaphylaxis, angioedema, respiratory distress, or urticaria), a single-dose combination of clindamycin with an aminoglycoside is a reasonable alternative for cesarean delivery prophylaxis.
- ▶ Infective endocarditis prophylaxis is not recommended for women with acquired or congenital structural heart disease for vaginal or cesarean delivery in the absence of infection, except possibly for the small subset of patients at highest potential risk of adverse cardiac outcomes. Those at highest risk are women with cyanotic cardiac disease, or prosthetic valves, or both. Mitral valve prolapse is not considered a lesion that ever needs infective endocarditis prophylaxis.
- ▶ A single dose of antibiotic at the time of repair is reasonable in the setting of obstetric anal sphincter injuries (OASIS).

The following recommendations are based primarily on consensus and expert opinion (Level C):

- ▶ Patients with lengthy surgical procedures (eg, greater than two drug half-lives of the antibiotic, which is 4

hours for cefazolin and measured from the initiation of the preoperative dose, not from the onset of surgery) or those who experience excessive blood loss (eg, greater than 1,500 mL) should receive an additional intraoperative dose of the same antibiotic given for preincision prophylaxis.

- A 1-g intravenous dose of cefazolin as prophylaxis before cesarean delivery may be considered for women weighing 80 kg or less. Increasing the dose to 2 g for patients weighing 80 kg or more is recommended; however, the benefit of administering 3 g in obstetric patients weighing 120 kg or more has not yet been established.
- Evidence is insufficient to recommend antibiotic prophylaxis for history-, ultrasonography-, or examination-indicated cervical cerclage.
- Routine screening of obstetric patients for MRSA colonization is not recommended. However, in obstetric patients known to be MRSA colonized, consideration may be given to adding a single dose of vancomycin to the recommended antibiotic prophylaxis regimen for women undergoing cesarean delivery.
- There are currently insufficient data in pregnant patients to warrant or recommend screening all women preoperatively for MRSA colonization status, particularly because most colonized patients will not develop invasive disease.

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1990–April 2018. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I Evidence obtained from at least one properly designed randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

Published online on August 22, 2018.

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Use of prophylactic antibiotics in labor and delivery. ACOG Practice Bulletin No. 199. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;132:e103–19.

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