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Optimizing Guideline-Recommended Antibiotic Doses for Pediatric Infective Endocarditis

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Abstract

The American Heart Association recently published an updated scientific statement on the management of infective endocarditis in childhood. The recommendations included for vancomycin, aminoglycoside, and β -lactam dosing and monitoring are based primarily on expert opinion and do not consider available evidence for dose optimization based on pharmacokinetic and pharmacodynamic principles in pediatric patients. This is concerning because even when clinically necessary, some practitioners may be hesitant to deviate from guideline-recommended doses. In this perspective, we highlight potential areas for improvement in the statement-recommended doses and summarize evidence supporting antibiotic dosing optimization. The addition of a pediatric clinical pharmacist with expertise in antibiotic dosing to the panel would be beneficial for future updates.

With the ever-expanding medical literature, well-formulated evidence-based guidelines, scientific statements, and recommendations are highly useful tools for clinicians. We were, therefore, pleased to find the publication of an updated American Heart Association (AHA) scientific statement for the management of pediatric infective endocarditis (IE) written by Baltimore et al¹ (referred to from here on as the 2015 IE Update), which was based both on evidence and expert opinion. However, given our clinical expertise with optimizing antibiotic dosing in children, we found a number of the recommendations to be less than ideal. When taking into account drug-specific pharmacokinetic (PK) and pharmacodynamics (PD) parameters as well as current medical evidence, it becomes clear that application of the guideline-recommended antibiotic doses could result in a suboptimal antibiotic regimen. Because PK/PD parameters were given significant weight in the adult endocarditis guidelines and recommendations, we find it perplexing that these variables were not considered in the pediatric patient population.² This is especially important given that antibiotic PK/PD characteristics in children can be quite different in comparison to the adult cohort.

For any infection, especially those that are difficult to treat, such as IE, the goal is to optimize antibiotic doses to meet PK/PD targets to increase the likelihood of positive patient outcomes while minimizing unnecessary toxicity and development of resistance. Established efficacy-associated PD parameters (Table 1) should be considered when recommending or administering an antibiotic regimen.^{3,4} Although limited, there is an increasing body of evidence suggesting positive outcomes associated with optimized dosing strategies that incorporate efficacy predictors such as length of time free drug concentrations exceed the minimum inhibitory concentration for the bacterial pathogen ($fT > MIC$), area under the curve for plasma

concentration relative to organism MIC (AUC:MIC), or maximum serum concentration relative to organism MIC (C_{max} :MIC). While the expertise of the authors involved in the 2015 IE Update is robust, a consensus on pediatric dosing is incomplete without including the opinion of a pediatric pharmacist expert. Pediatric clinical pharmacists with expertise in infectious diseases positively affect patient care through their knowledge and experience in optimizing antibiotic dosing based on PK/PD parameters, and their opinions should be solicited and included during the development of organizational guidelines and recommendations.⁵⁻⁸ We appreciate the suggestion to consult pharmacists in certain circumstances found in the footnotes to table 7 in their article and in the section regarding antibiotic blood levels. However, in the case of the 2015 IE Update, a pediatric pharmacist was not included in the panel, which may be a reason for omitting PK/PD considerations within their recommendations and dosing algorithms.

Table 1. Optimized Dosing Strategies Utilized at the Authors' Institution.

Antibiotic	PD Predictor of Efficacy	Recommended Dosing ^a	Additional Considerations and TDM	References
Vancomycin	AUC:MIC \geq 400:1	<ul style="list-style-type: none"> Individualize dose based on consideration of risks/benefits, severity of illness, underlying disease states, renal function status and maturity, MIC of offending organism, results of TDM Previously healthy children or children with adequate renal function: 15 mg/kg IV Q 6 hours Previously healthy adolescents or adolescents with good renal function: 15-20 mg/kg IV Q 8 hours Infants with hemodynamically significant CHD or s/p CPB: 15 mg/kg IV Q 8 hours 	<ul style="list-style-type: none"> Controversy exists regarding optimal monitoring strategy for vancomycin Suggest using AUC monitoring (2-concentration strategy with calculation or Bayesian software strategy) when possible for vancomycin monitoring When using trough concentrations for monitoring, clinicians adjusting doses should utilize guideline-recommended goals while accounting heavily for patient status and recognizing lack of strong correlation between trough and AUC 	9-13
Gentamicin and tobramycin	C_{max} :MIC 10:1	<ul style="list-style-type: none"> GN: 7-8 mg/kg IV once daily GP: 3-6 mg/kg IV once daily (or divided tid for treatment of enterococci) 	Goal trough for EIA: undetectable for 4-6 hours	4
Cefepime	\geq 70% fT>MIC	<ul style="list-style-type: none"> 50 mg/kg (up to 2000 mg) IV Q 8 hours Infuse over 3-4 hours Consider Q 6 hour dosing if unable to utilize extended infusions 	<ul style="list-style-type: none"> If unable to use extended infusions, Q8 still preferred over Q12 Can also be given as a continuous infusion; consider TDM using reference lab to optimize individual dosing 	8, 15
Piperacillin/Tazobactam	\geq 60%, fT>MIC	<ul style="list-style-type: none"> 112.5 mg/kg (up to 3375 mg) IV Q 8 hours, infused over 3-4 hours, or 84.4 mg/kg (up to 3375 mg) IV Q 6 hours, infused over 30 minutes 	Can also be given as a continuous infusion; consider TDM using reference lab to optimize individual dosing	7, 15, 18
Nafcillin	\geq 60%, fT>MIC	200 mg/kg/d (up to 12 g) Administered as a continuous infusion		3, 4
Penicillin G	\geq 60%, fT>MIC	300 000 units/kg/d (up to 24 million units) Administered as a continuous infusion		3, 4

Abbreviations: AUC:MIC, area-under-the-curve to minimum inhibitory concentration ratio; CHD, congenital heart disease; C_{max} :MIC, maximum serum concentration to minimum inhibitory concentration ratio; CPB, cardiopulmonary bypass; EIA, extended-interval aminoglycosides; fT>MIC, free time over minimum inhibitory concentration; GN, Gram-negative; GP, Gram-positive; IE, infective endocarditis; IV, intravenous; PD, pharmacodynamic; Q, every; s/p, status post; TDM, therapeutic drug monitoring.

^aAll dosing should be individualized with consideration for the MIC of known or potential organisms; patient factors, including renal function; and consideration for risks and benefits. Neonatal dosing is not provided in this table, given the lack of inclusion in the 2015 IE Update. We recommend determination of optimal and patient-specific doses via consultation with neonatal and infectious diseases pharmacy specialists with special consideration for developmental pharmacokinetic differences.

Vancomycin

We agree that the vancomycin dosing recommendation of 60 mg/kg/d divided every 6 hours is appropriate for many children, but a combination of factors, including comorbidities, renal function, and severity of illness, should be considered when choosing initial vancomycin regimens. A 6-hour dosing interval is likely unnecessary and potentially harmful for some children, particularly those with hemodynamically significant congenital heart disease and renal dysfunction or for children 11 years of age and older. PK modeling suggests that in children with congenital heart disease, doses between 30 and 40 mg/kg/d, rather than 60 mg/kg/d recommended by the 2015 IE Update, predict trough vancomycin concentrations of approximately 12 to 16 mg/L.⁹ Because of the underlying disease state, greater PK variability is also observed in these patients.¹⁰

The 2015 IE Update recommends a maximum daily vancomycin dose of 2 g without supporting evidence, and we posit that using the recommended maximum may result in suboptimal AUC:MIC exposures for many patients. For the treatment of streptococci and staphylococci, including MRSA (methicillin-resistant *Staphylococcus aureus*), the dosing recommendation in the 2015 IE Update is 40 mg/kg/d divided every 8 to 12 hours. There is evidence, particularly with MRSA, that 40 mg/kg/d is often inadequate to achieve desired AUC:MIC exposures.^{11,12} Our personal experience in dosing and monitoring vancomycin in children would support that 40 mg/kg/d divided every 8 to 12 hours is insufficient for most patients, with previously mentioned exceptions. Furthermore, the discussion of vancomycin therapeutic drug monitoring (TDM) highlights only trough concentration monitoring, leaving out the importance of AUC:MIC target attainment. Positive outcomes with vancomycin are best predicted by achievement of an AUC:MIC of $\geq 400:1$, which may or may not be accurately predicted by trough concentrations in children.¹³ Area under the curve monitoring, using 2 concentrations or Bayesian software, may be a more appropriate monitoring parameter for efficacy.¹³ Although it is recognized that other dosing references may be more appropriate for in-depth discussions and drug dosing recommendations, the 2015 IE Update as written gives the impression that the contained information is sufficient for provision of care of all pediatric patients. Important additions to the vancomycin TDM risk-benefit discussion include the lack of studies in children correlating attainment of trough concentration targets with efficacy and evidence that higher trough concentrations (≥ 15 mg/L) may be associated with acute kidney injury.¹³⁻¹⁵

Aminoglycosides

The 2015 IE Update acknowledges that extended-interval aminoglycosides (EIA) are frequently used and are recommended by a similar adult panel but state that a recommendation for EIA in children cannot be made because of lack of evidence.¹ This optimized dosing strategy can and should be used in children as well as in adults (Table 1). Interestingly, the recommended aminoglycoside dosing provided in table 7 of the 2015 IE Update is the same for Gram-negative enteric bacilli and Gram-positive organisms at 3 to 6 mg/kg/d despite different peak serum concentration goals. It is acknowledged later in the antibiotic blood level monitoring section that higher doses (7.5 mg/kg/dose) may be needed to attain the desired peak concentration for Gram-negative organisms, but this is not reflected in the table. Furthermore, this section on goal monitoring provides goal peak and trough recommendations without regard to the MIC of the offending organism, despite a goal $C_{\max} : \text{MIC}$ ratio of 10:1 for Gram-negative pathogens.⁴ Undetectable concentrations at the end of the interval provide reduced likelihood of

nephrotoxicity regardless of dosing regimen.⁴ Evidence to support goal gentamicin peak concentrations in the treatment of endocarditis is based on in vitro and animal data, and further studies are needed.

β-Lactams

Cefepime is a time-dependent bactericidal antibiotic with optimal efficacy determined by $fT > MIC$, but it has a relatively short half-life and one that is shorter in children than in adults.¹⁶ Because IE can be so difficult to treat, we assert that based on simulated PD target data, cefepime should be dosed no less than every 8 hours in individuals with normal renal function, particularly when pathogen MICs are 1 or greater.¹⁷ This is of particular importance, given that adequate treatment of many pathogens with cefepime requires aggressive dosing and the implementation of “susceptible dose-dependent” as an interpretive criteria.¹⁸ Specifically, *Enterobacteriaceae* with cefepime MICs of 4 and 8 mg/L are more likely to experience clinical failure when treated with cefepime in low doses, so aggressive dosing is warranted.¹⁸

Piperacillin/tazobactam is also a time-dependent bactericidal antibiotic with a short half-life.¹⁹ Published PK/PD data do not support the 2015 IE Update recommended dosing of 240 mg/kg divided every 8 hours, on the basis that it is suboptimal and unlikely to provide desired target attainment, particularly for pathogens with elevated MICs.^{17,20} The 2015 IE Update seems to apply PK/PD concepts with ampicillin/sulbactam dosing recommendations (every 4 hours), but the paradigm does not appear to have been considered for piperacillin/tazobactam and cefepime. In patients with normal renal function, we do not believe that piperacillin/tazobactam is optimally dosed at every 8-hour dosing unless given as an extended infusion. We promote dose and infusion optimization based on the organism MIC. Though comparative outcomes data are limited, delivery of antibiotics such as penicillin and nafcillin by continuous infusion is an administration strategy that may provide consistent concentrations at the site of infection while limiting frequent manipulation of the IV catheter, which is known to increase the risk of infection, and limiting the number of doses required to be administered by nursing and prepared by the pharmacy department.²¹

Conclusions

The 2015 IE Update includes antibiotic dosing recommendations that generally should be considered in context to each patient; it is not a binding document requiring strict adherence. There can be a hesitance to deviate from guideline recommendations in part because it is difficult for a provider to critically evaluate and distinguish between the recommendations derived from quality studies and those from a consensus of experts. The discussion surrounding dosing recommendations in the 2015 IE Update is limited and further impairs the general provider by creating uncertainty regarding the availability or absence of supporting rationale for a specific recommendation, such as the maximum dose for vancomycin. In the absence of clear rationale, the provider is likely to either follow the evidence with which they are acquainted or to follow the recommendations of the expert panel, which may be inadequate and/or ultimately harmful to many pediatric patient populations.

There is an opportunity to improve the antibiotic dosing recommendations contained within the 2015 Pediatric Infective Endocarditis Update.¹ We have highlighted our areas of disagreement with the 2015 IE Update and included optimized dosing strategies for these antibiotics in Table

1. Efforts can be taken to bridge the gap between the quest for evidence-based recommendations in the setting of limited well-designed comparative studies and expert-based opinions that result in suboptimal dosing based on existing PK/ PD data. Inclusion of a pediatric pharmacist expert in the development of antibiotic dosing recommendations contained within guidelines could be an appropriate first step and would broaden the overall perspective of the expert panel. We recommend that the AHA involves a pediatric pharmacist with expertise in optimizing antibiotic dosing, specifically considering PK/PD differences throughout the pediatric developmental continuum, in future updates of this guideline or any guideline in which antibiotic doses are recommended. We also recommend that prescribers and pharmacists providing care for children with endocarditis consider the origin of guideline-recommended antibiotic doses while balancing knowledge of fundamental PK/PD principles and available evidence.

Declaration of Conflicting Interests

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