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ARTICLE

Early onset sepsis calculator-based management of newborns exposed to maternal intrapartum fever: a cost benefit analysis

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Abstract

Objective To determine potential net monetary benefit of an early onset sepsis calculator-based approach for management of neonates exposed to maternal intrapartum fever, compared to existing guidelines.

Study design We performed a cost-benefit analysis comparing two management approaches for newborns ≥34 weeks gestational age exposed to maternal intrapartum fever. Probabilities of sepsis and meningitis, consequences of infection and antibiotic use, direct medical costs, and indirect costs for long-term disability and mortality were considered.

Results A calculator-based approach resulted in a net monetary benefit of $3998 per infant with a 60% likelihood of net benefit in probabilistic sensitivity analysis. Our model predicted a 67% decrease in antibiotic use in the calculator arm. The absolute difference for all adverse clinical outcomes between approaches was ≤0.6%.

Conclusions Compared to existing guidelines, a calculator-based approach for newborns exposed to maternal intrapartum fever yields a robust net monetary benefit, largely by preventing unnecessary antibiotic treatment.

Introduction

Fetal exposure to chorioamnionitis is associated with a variety of neonatal complications, including early-onset infection [1, 2]. In 2002, the Centers for Disease Control and Prevention (CDC) recommended empiric broad-spectrum antibiotic therapy for all asymptomatic infants born to women who had received intrapartum antibiotics for suspected chorioamnionitis [1]. In 2010, CDC's revised guideline further expanded this recommendation to include asymptomatic newborns exposed to chorioamnionitis, regardless of whether maternal intrapartum antibiotics had been administered [3]. The 2010 revision cited data, which suggested that the incidence of maternal intrapartum fever and chorioamnionitis were essentially equivalent, noting as well the importance of consultation with obstetric providers for guiding neonatal management. It further recommended that at minimum, a complete blood count and blood culture be obtained, even in the absence of other risk factors and clinical signs of early-onset sepsis (EOS). Subsequently, the American Academy of Pediatrics' Committee on Fetus and Newborn (AAP-COFN) issued a report in 2012, followed by further commentaries, which reiterated CDC's recommendations for chorioamnionitis-exposed newborns [4, 5].

Contemporaneous data on the effectiveness of these neonatal management strategies, however, are not robust [5, 6] and therefore substantial variability in clinical practice exists [5, 7]. Moreover, unnecessary diagnostic testing and/or therapy has important biosocial implications for the patient, his/her family, and society, such as impacts on hospital length of stay, maternal-infant bonding, breastfeeding success, and harm related to diagnostic procedures and therapies [5, 6].

Acknowledging many of these concerns, a National Institute of Child Health and Human Development expert panel and ACOG's Committee on Obstetric Practice have both issued statements on chorioamnionitis that cite a sepsis risk calculator-based approach to enable more judicious use

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of empiric antibiotics in asymptomatic newborns [8, 9]. In this paradigm, the management of neonates is guided by the use of a validated EOS calculator that incorporates highest intrapartum temperature among five other maternal variables, in conjunction with serial clinical evaluation in the immediate postnatal period [10–12].

The potential population-level clinical and economic impacts of a calculator-based approach to the management of asymptomatic newborns exposed to intrapartum maternal fever are unknown. We performed a cost-benefit analysis (CBA) from the U.S. societal perspective to compare this approach to prevailing CDC/AAP consensus recommendations.

Methods

We performed a CBA using a decision tree to model the clinical course of well-appearing infants ≥34 weeks gestational age exposed to maternal intrapartum fever (a subset of the target population for the calculator-based management approach) [10–12]. We chose a CBA over a cost-utility analysis to allow complete consideration of the clinical and economic implications of each management strategy, particularly given the difficulty in ascertaining quality-of-life for neonatal outcomes, and assignment of health state utilities to neonates [13, 14].

We defined empiric antibiotic use as administration within the first 12–24 h of life, in most instances requiring further diagnostic evaluation and treatment. Otherwise, infants were assumed to receive routine care unless she/he became ill-appearing, thus requiring antibiotic administration. Once empiric antibiotic therapy is started in either approach, it is continued for at least 48 h, by which time the bacteria will be detected in >98% of cultures, if present [15–18]. The base case treatment duration equaled the length-of-stay (LOS) derived from Healthcare Cost and Utilization Project (HCUP) data: median LOS for non-bacteremic septicemia was 2 days, bacteremia 7 days (mean 11.9 days), and meningitis 14 days (mean 15.7 days); these durations approximate the duration of therapy reported in published literature [7, 19]. We calculated the antibiotic utilization rate as total antibiotic days per 1000 patient-days.

We included adverse outcomes that have quantifiable clinical and economic impacts over the lifetime of the affected individual. The most clinically significant antibiotic-related adverse effects among newborns are reversible nephrotoxicity and permanent sensorineural hearing loss due to aminoglycoside exposure [20, 21]. Infants who survive meningitis may suffer permanent neurocognitive deficits, such as intellectual disability, cerebral palsy, and hearing loss, among others, thus we did not explicitly include ototoxicity as a separate outcome for these infants [19, 22, 23]. Neurocognitive deficits were not explicitly included for CSF(−) individuals as existing data are inadequate to assign an estimate of neurocognitive disability directly attributable to sepsis, and there are no robust data demonstrating that neurocognitive disability (excluding potential drug-induced ototoxicity) results from clinical or culture-proven EOS in the absence of meningitis [22]. However, we included post-discharge readmission because a proportion is related to infection that could then lead to similar long-term outcomes of death, neurocognitive disability, or healthy at discharge [24]. We did not incorporate antibiotic-associated hypersensitivity reactions, (permanent) nephrotoxicity, neurotoxicity, and myelosuppression as these are rare and/or reversible.

All probabilities noted in Fig. 1 are defined in Table 1. We derived probabilities of EOS, meningitis, readmission, long-term sequelae of meningitis or drug-induced ototoxicity, and attributable mortality from published literature, with the last verified using data from the HCUP National Inpatient Sample (NIS) [11, 20–31]. In the base case analysis, we attempted to account for the possibility that 48 h of empiric antibiotics would prevent some proportion of asymptomatic and initially culture-negative newborns from subsequently developing clinical sepsis and/or culture-positive disease, as substantiated by limited historical data; this risk of developing disease is designated γ in our model [32, 33]. A prime superscript, γ', was used to designate the corresponding probability of ill-appearance/clinical sepsis or positive blood culture among infants who do not receive initial empiric antibiotics, regardless of management strategy. As described below and shown in column 4 of Table 1, subsequent sensitivity analyses used identical ranges of values for γ and γ'.

Direct costs associated with hospitalization were based on HCUP cost data by ICD9 diagnosis code, which include national estimates of direct costs associated with management for each diagnosis, including adverse drug reactions, medication errors, procedure complications (e.g. IV infiltration), and hospital-acquired infections [25]. We used ICD9 codes for healthy newborns weighted for percentage delivered via Cesarean section (31.9%) [34] and for those diagnosed with septicemia or streptococcal or gram-negative meningitis receiving antibiotic therapy (Table 1). We weighted costs for meningitis by pathogen according to their relative prevalence in HCUP, contemporary epidemiologic data, and etiology-specific recommendations for minimum duration of therapy, to calculate an average composite cost of hospitalization [19, 23, 30]. We excluded *Listeria monocytogenes* as it has become very uncommon in the U.S. [35]; further, the 2000–2014 HCUP data reported no cases of listeriosis (ICD9 027.0) among neonates. Indirect costs for aminoglycoside-associated ototoxicity and neurocognitive disability included lifetime costs of healthcare and special education services attributable to these

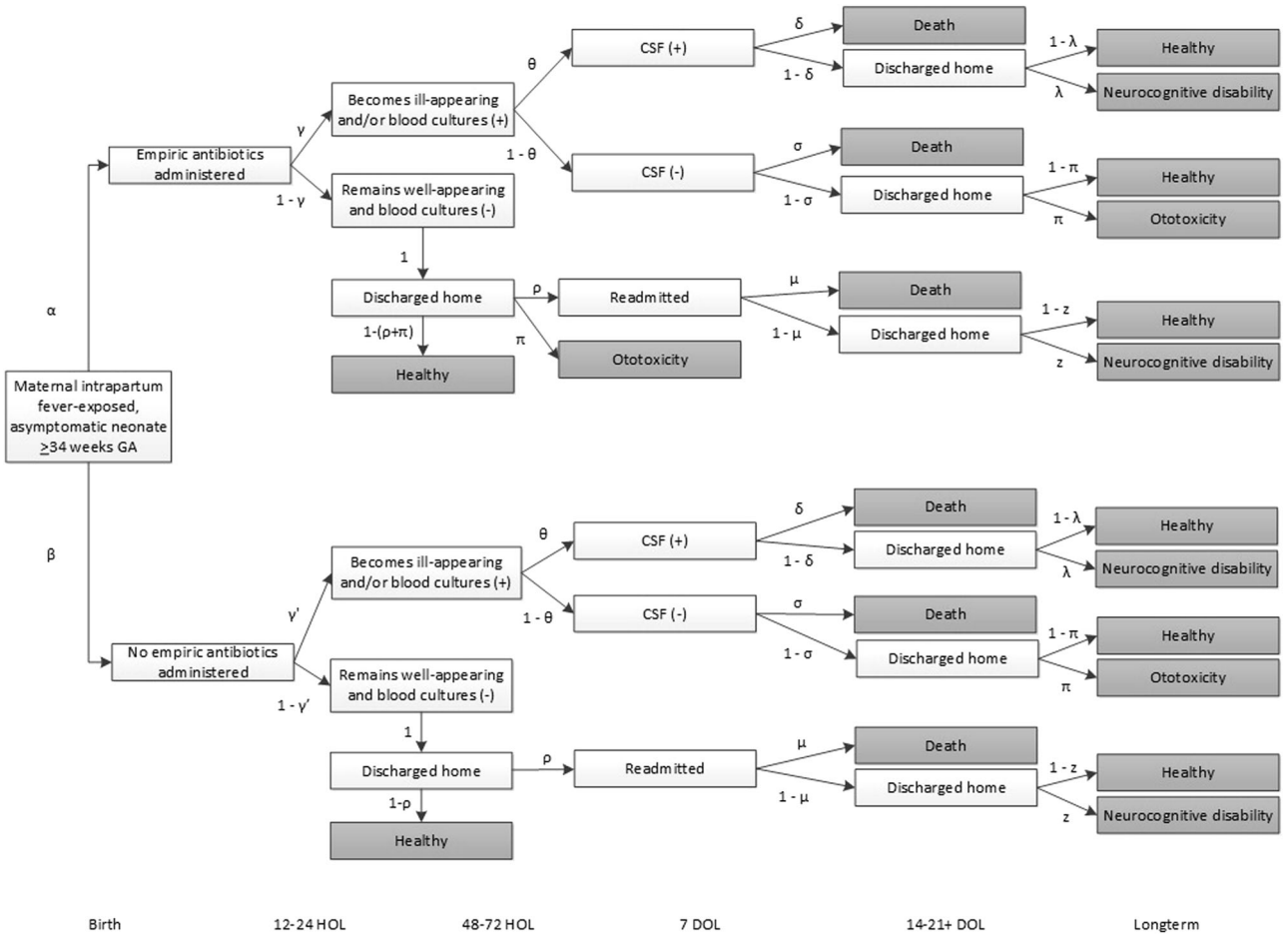

Fig. 1 Decision model—clinical course and management of asymptomatic term and late preterm newborns exposed to maternal intrapartum fever. Under the CDC (2010) and AAP (2012) guidelines, most (if not all) chorioamnionitis-exposed neonates will receive empiric antibiotics at birth. In the calculator-based management approach, most chorioamnionitis-exposed neonates will not receive empiric antibiotics at birth, remaining under observation with or without limited evaluation (e.g. blood culture), following the branch on the bottom half of the decision tree. Neurocognitive disability includes mental retardation, cerebral palsy, hearing loss, and vision impairment. *HOL* hours of life, *DOL* days of life

sequelae, as well individual economic productivity losses into adulthood [36, 37]. We used HCUP costs and LOS to estimate overall costs for newborns admitted for antibiotic therapy and subsequently discharged after 48–72 h. We used median costs for the base case, and the expected minimum and maximum LOS to estimate the upper and lower bounds of the range of costs.

The value of a life lost due to neonatal disease in the base case was $7 million, inflated to $9.6 million in 2017 US Dollars [14, 38–40], a range also used in economic valuations by the U.S. Environmental Protection Agency to analyze the impact of public policies on health [41]. We subjected this parameter to threshold analysis (holding other model inputs constant), to identify the value at which the NMB of calculator-based management reaches equipoise with the CDC/AAP consensus approach.

Table 1 includes all probabilities and costs used to calculate the cost-benefit per infant of calculator-based management vs. the CDC/AAP consensus approach. Costs were converted to 2017 US Dollars using the Medical Consumer Price Index [39]. We conducted one-way sensitivity analysis to determine the relative influence of each model parameter by varying one parameter at a time [39, 41] and probabilistic sensitivity analyses using 10,000 Monte Carlo simulations to further evaluate uncertainty. Given the absence of discrete data on the distribution of each parameter estimate, all parameters were varied according to a triangular distribution, which only requires a minimum, maximum, and mode of a parameter, as per ranges reported in the literature.

The HCUP data for bacteremia of specific etiology are limited to those <1 year of age as a group and not for newborns specifically. We therefore could not directly assess the possibility that newborns with a positive blood culture may have different risks of selected negative clinical

Table 1 Decision model inputs

Parameter	Health state	Cost	Range	ICD9 Code[a]	Reference
α	Antibiotics given	$3,933[b]	$3,933–19,663	V29.0	[25]
β	No antibiotics given	$1,143	$910–3,402	V30.00, V30.01	[25, 34]
γ, γ′	Blood culture (+)	$11,917	$8,512–23,833	771.81	[25]
	Blood culture (−)	$3,933	$3,933–19,663		[25]
θ	Cerebral spinal fluid culture (+)	$24,117	$15,961–33,518	320.2, 320.82	[25]
	Cerebral spinal fluid culture (−)	$11,917	$8,512–23,833		[25]
ρ	Readmission	$5,093	$428–35,593		[24]
λ	Neurocognitive disability	$1,087,960	$828,668–1,619,117		[37]
π	Ototoxicity	$393,151	$42,366–828,668		[37]
δ, σ, μ	Mortality	$9,653,532	$5,516,304–13,790,761		[38, 40]

Parameter	Health State	Probability	Range	ICD9 code	Reference
$\alpha_{CDC/AAP}$	Antibiotics given – CDC/AAP	0.80	0.65–1		[3, 28, 29, 31, 48]
$\alpha_{calculator\text{-}based}$	Antibiotics given – calculator – based	0.10	0.025–0.25		[11, 29]
β	No antibiotics given	$=1-\alpha$			
γ	Ill-appearing OR blood culture (+)	0.029	0.007–0.049		[28, 29, 32, 33]
	Well-appearing AND blood culture (−)	$=1-\gamma$			
γ′	Ill-appearing OR blood culture (+)	0.0375	0.007–0.049		[29, 33]
	Well-appearing AND blood culture (−)	$=1-\gamma'$			
θ	Cerebral spinal fluid (+)	0.02	0.013–0.098		[11, 30, 31]
	Cerebral spinal fluid (−)	$=1-\theta$			
ρ	Readmitted – antibiotics given	0.0179	0.0148–0.0215		[24]
λ	Neurocognitive disability	0.19	0.17–0.235		[22, 27]
z	Neurocognitive disability – readmission	0.0016	0.00097–0.01		[22, 24, 27]
π	Ototoxicity	0.014	0.005–0.023		[20, 21, 47]
δ	Mortality – CSF (+)	0.040000	0.0293–0.071	320.2, 320.82	[23, 25]
σ	Mortality – CSF (−)	0. 0311	0.016–0.0462	320.2, 320.82	[25]
μ	Mortality – readmission	0.00117	0–0.0023	V30.0	[25]

[a]ICD9 codes for which data regarding the corresponding health state were derived from the HCUP National Inpatient Sample data are listed. For β (no antibiotics given), costs were weighted 31.9% for Cesarean section to account for the number of babies born via this method, based on CDC Birth Statistics

[b]Cost of hospitalization (α) for asymptomatic newborns admitted for "rule-out EOS" (LOS 48–72 h) derived from blood culture (+) (γ), as described in Methods

outcomes compared to those that do not. Further, two small single center U.S. studies did not identify such differences [42, 43], and the U.S.-based data suggest that clinical management and utilization outcomes are similar for culture-negative infants compared to treatment recommendations for bacteremic newborns. We chose, however, to model this possibility in a secondary analysis in which we imputed the "best" and "worst" case extremes of the ranges for meningitis (θ) and mortality (σ) as noted in Table 1 to generate cost-benefit and probabilistic estimates. We included an additional analysis setting the likelihood of an asymptomatic neonate becoming ill-appearing or bacteremic to be equivalent regardless of empiric antibiotic administration (i.e. $\gamma = \gamma'$) to account for situations in which empiric antibiotic exposure may not have had an impact whatsoever.

Finally, we estimated the cumulative incremental net benefit in the U.S. per year with increasing levels of adoption of the calculator-based management approach, in the base case. All calculations were performed using Microsoft Excel, 2016.

Results

In the base case, the total direct and indirect cost per infant exposed to maternal intrapartum fever was $13,766 for calculator-based management, compared to $17,764 under

the CDC/AAP consensus approach, yielding an incremental net benefit per infant of $3998 in favor of calculator-based management. Total direct costs for acute medical care were $1781 and $3711 per infant for each algorithm, respectively, again favoring the calculator-based management approach with a net per-patient benefit of $1930 in direct medical costs alone.

One-way sensitivity analyses show that the probability of developing clinical signs and symptoms of infection and death, followed by costs associated with mortality or ototoxicity, had the greatest influence on the observed net benefit in favor of the calculator-based management approach (Fig. 2). In 90% of one-way simulations, there is a net benefit with use of the calculator-based management approach, ranging from $40 to $12,524. In rare instances, there is a net cost of up to $1466. A net benefit was predicted with calculator-based management if the proportion of infants receiving empiric antibiotics under the CDC/AAP consensus approach remained at or above 6.9% (in comparison to a base case of 80%, which was chosen in the absence of robust contemporary data to estimate the adherence to existing recommendations). Indeed, regardless of the probability of receiving antibiotics under either management strategy (ranging from 65–100% under CDC/AAP guidelines, vs. 2.5–25% under calculator-based management), the net monetary benefit persisted under the calculator-based approach.

In the base case, only 134 infants per 1000 livebirths managed under the calculator-based approach require antibiotic therapy and monitoring, compared with 808 infants under CDC/AAP, a 67.4% decrease. This care resulted, in the base case, in a burden of total antibiotic utilization of 220 and 824 antibiotic days per 1000 patient-days for the calculator-based management and CDC/AAP consensus approaches, respectively. In the base case, the calculator-based management approach was associated with <0.6% absolute change in incidence for each adverse clinical outcome compared to the CDC/AAP consensus. Under the calculator-based management approach, our model predicted fewer cases of ototoxicity and readmission, but slightly more cases of meningitis, clinical sepsis/bacteremia, and all-cause mortality (Table 2). In one-way sensitivity analysis for aminoglycoside-associated ototoxicity (the clinical outcome with the greatest absolute percent change), imputing a value of 0% (i.e. no risk of ototoxicity) from a base case of 1.4% still resulted in a per-infant net benefit of $111 favoring the calculator-based approach.

Per 1000 live-births, probabilistic sensitivity analysis yielded the following outcomes for calculator-based management vs. CDC/AAP consensus, respectively: median 2.01 [1.26–2.7] vs. 1.55 [1.01–2.04] deaths due to EOS or meningitis; 2.12 [1.09–3.55] vs. 1.64 [0.88–2.69] cases of meningitis; 52.54 [39.57–62.22] vs. 40.35 [31.5–46.82] cases of sepsis/bacteremia; 0.47 [0.24–0.81] vs. 0.38 [0.2–0.65] cases of neurocognitive disability due to early-onset meningitis; 3.18 [1.92–4.49] vs. 15.39 [11.34–18.81] cases of ototoxicity; 18.16 [17.17–18.91] vs. 18.42 [17.35–19.24] readmissions; and 184.17 [140.4–224.37] vs. 871.64 [810.24–918.29] admissions for antibiotic therapy. In probabilistic sensitivity analysis, management according to the calculator-based management approach yielded a net benefit in 60% of simulations. The median NMB per infant was $5966 (mean $6475) with a 95% range from $54,000 in NMB to $41,000 in net cost (Fig. 3).

For our secondary analysis, we found that a worst-case scenario (i.e. highest downstream clinical risks for negative outcomes, θ and σ), yielded a net benefit of $3046 per infant in favor of the calculator-based strategy, with a 57.4% likelihood of persistent net benefit in probabilistic sensitivity analysis (PSA). In the best-case scenario for this population (i.e. lowest downstream risks for negative outcomes), the net benefit increased to $4871, with a 74.1% likelihood of persistent net benefit in PSA. Setting the likelihood of an asymptomatic neonate becoming ill-appearing or bacteremic to be equal between antibiotic-exposed vs. no antibiotics ($\gamma = \gamma'$) led to a net benefit of $5850 in favor of the calculator-based approach, with no differences in the number of cases per 1000 livebirths for each clinical outcome, except ototoxicity (1.74 vs. 11.26 per 1000 livebirths), and a 68.9% likelihood of net benefit in PSA.

Among an estimated 3,978,497 live births in 2015 [44], 97.2% are of gestational age $\geq$34 weeks and approximately 3.3% are exposed to maternal intrapartum fever [3]. Therefore, using results from our base case analysis, we estimate 127,614 infants exposed to maternal intrapartum fever each year, yielding $459 million in societal net monetary benefit per year if 90% of clinicians used calculator-based management instead of the CDC/AAP consensus approach. At 10% adoption of calculator-based management by clinicians, $51 million per year in NMB is predicted; with 100% adoption, up to $510 million.

Discussion

Our results suggest that use of a calculator-based management approach for newborns exposed to intrapartum fever yields a NMB of nearly $4000 per infant compared to management according to existing CDC and AAP guidelines. Nearly half of this benefit is derived from avoidance of empiric antibiotic use and monitoring. This reflects our observation that ~10% of neonates managed per the calculator-based approach would require more intensive medical management, compared to ~80% of neonates under the CDC/AAP approach, per our base case. It has been

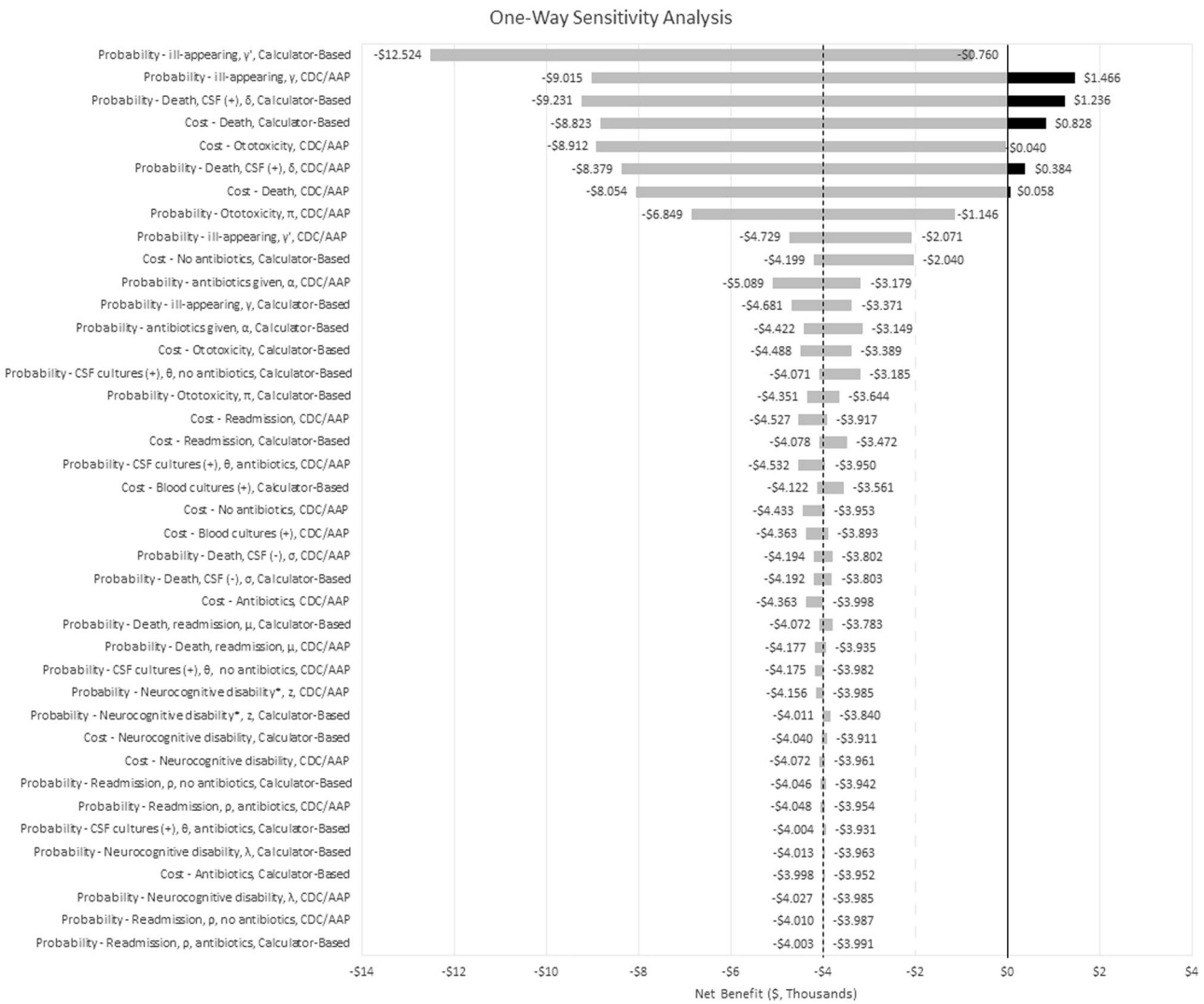

Fig. 2 One-way sensitivity analysis. The range of net benefits is shown in thousands of dollars. Gray bars signify net monetary benefits under the calculator-based strategy. The dotted line represents the base-case net benefit of $3,998. Situations for which there is a net cost under the calculator-based approach are shown in black bars, depicted to the right of the vertical black line, which represents equipoise between the two strategies (i.e. net benefit = $0). Ranges for each parameter can be found in Table 1. *Represents neurocognitive disability resulting from readmission

frequently suggested that too many neonates born of mothers with intrapartum fever are receiving diagnostic evaluation and antibiotics [5, 6]. Our analyses provide first evidence that adoption of a validated, calculator-based management approach would provide substantial NMB when applied to the U.S. birth cohort.

Our base case NMB results were robust in all sensitivity analyses and consistent with clinical expectations and the published literature. In the one-way sensitivity analysis, calculator-based management was associated with higher costs only at extreme and unrealistic inputs for development of signs/symptoms of infection and likelihood of death due to infection (for example, it is unrealistic for antibiotic-exposed infants managed under the CDC/AAP guidelines to have a differential risk of developing clinical signs/symptoms of illness compared to antibiotic-exposed infants under a calculator-based strategy). Further, when the clinical outcome with the largest absolute difference in incidence (ototoxicity) was set to zero, NMB persisted, albeit at a low value per infant. In the probabilistic sensitivity analysis, per-infant NMB was found in 60% of the simulations. Finally, we found that the NMB threshold (the transition point to net cost) was reached only at unrealistically low levels of empiric antibiotic use in the CDC/AAP consensus approach (<7%) or at a very high cost for lost neonatal life (>$31 million) which far exceeds the accepted values typically used in economics literature and government policy practices [38, 40, 41].

Herein we present the first estimates of the burden of antibiotic use avoided with adoption of a calculator-based

Table 2 Base case clinical outcomes[a]

Outcome	CDC/AAP[b]	Calculator-based approach[b]	Absolute difference (%)	Excess cases per year in U.S.[c]
Antibiotic therapy given	808	134	−67.38%	−85980
Ototoxicity	11.28	1.85	−0.94%	−1203
Clinical sepsis/bacteremia	30.70	36.66	0.60%	760[d]
Meningitis	0.61	0.73	0.01%	15
All-cause mortality	0.98	1.17	0.02%	24
Readmission	17.35	17.24	−0.01%	−14
Neurocognitive disability	0.14	0.16	0.00%	3

[a]Because results of base case analysis are generated from a model, the methodology used do not permit standard population-based estimates of dispersion (e.g. 95% CI). Interquartile ranges calculated in probabilistic sensitivity analysis are reported for each clinical outcome in the Results section.

[b]Number of cases reported as median number per 1000 neonates born to a mother with intrapartum fever.

[c]Based on an expected total of 127,614 maternal intrapartum fever-exposed infants per year.

[d]Per published literature, some 4–40% of babies with this ICD9 code is blood culture positive (30–304 neonates in our base case/year in the U.S.). Refer to Discussion for details

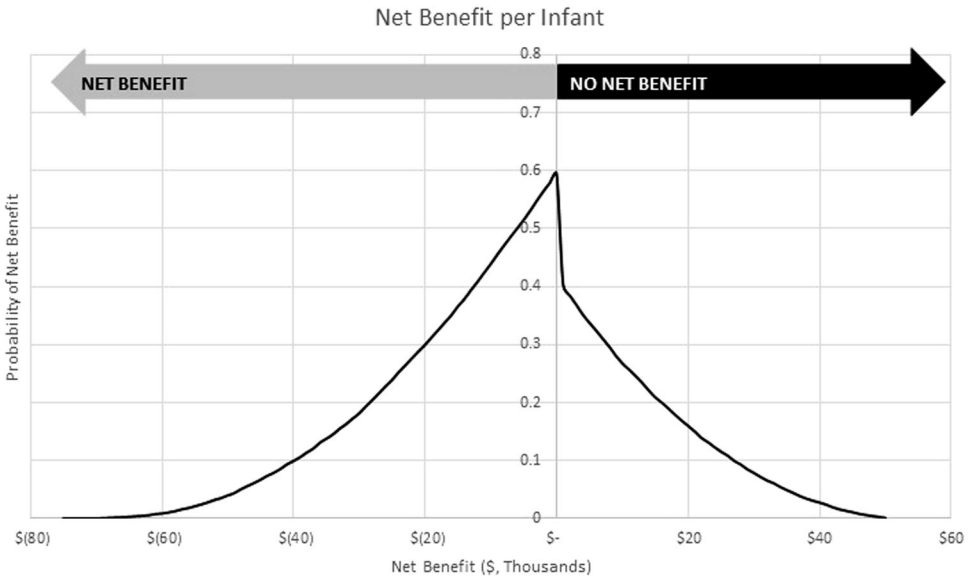

Fig. 3 Probabilistic sensitivity analysis (likelihood of net benefit). There is a 60% probability of NMB, and a 50% probability that the NMB will be at least $6,000 per infant. There is a 40% probability of no net benefit or net increased costs under calculator-based management vs. the CDC/AAP consensus approach. There is a 27% probability that the calculator-based management approach will result in net costs >$10,000 per infant

management approach among the US cohort of neonates exposed to maternal intrapartum fever. Use of the EOS calculator necessarily reduces the number of asymptomatic infants that receive empiric antibiotics since it targets only those with an elevated prior probability of sepsis, whereas the CDC/AAP guidelines make no such distinction amongst newborns exposed to intrapartum fever. Existing EOS calculator studies have determined that 2–4% of all newborns, regardless of the presence or absence of maternal fever, would receive empiric therapy [10, 11, 29]. Three studies have specifically focused on application of the EOS calculator only to newborns exposed to chorioamnionitis, finding that between 2.5 and 25% of such infants would have received empiric antibiotics under the calculator-based management strategy [29, 45, 46]. We chose a base case of 10% antibiotic use (ranging to 25%) to include only those babies with exposure to maternal fever, as well as to reflect different degrees of non-adherence to a calculator-based management paradigm across different centers and patient populations.

We observed an absolute change in incidence for all clinical outcomes of <1% between the calculator-based management and CDC/AAP approaches. The largest absolute difference was observed for ototoxicity (−0.94%), due

to substantially less aminoglycoside exposure in the former approach. Overall, hearing loss is detected in 0.5–2.3% of neonates who receive aminoglycosides [20, 21, 47]. The 84% relative decline in incidence we observed highlights the impact of aminoglycoside use, despite the possible existence of co-morbidities associated with hearing loss in some patients. Our data were not sufficiently robust to evaluate other known antibiotic-associated complications such as renal damage, drug-drug interactions, and development of bacterial resistance.

Our models also predict slightly more cases per year of meningitis, sepsis, and death using the calculator-based management approach. We acknowledge that this risk may lead to challenges with widespread implementation of this strategy and that no algorithm should replace sound clinical judgement. However, the 760 excess U.S. cases of sepsis in the calculator-based approach include those with either bacteremia or clinical sepsis (culture negative). Others have shown that only 4–40% of such patients are blood culture positive, equivalent to 30-304 excess bacteremic newborns in our base case [28, 29, 33]. Similarly, data extrapolated from studies of the calculator indicate that only 0.2–1% of fever-exposed newborns are blood culture positive, representing 7–34% of our base case of newborns with clinical sepsis and/or bacteremia. Thus, we believe our estimate of these excess cases is a conservative over-estimate. As well, our observed number of excess cases may include zero, as shown in our probabilistic analysis. Given that the number of cases of meningitis and mortality are conditional on the likelihood of sepsis, we believe that our estimate of these excess cases is also a conservative over-estimate. Nonetheless, any increase in attributable neonatal morbidity and mortality is regrettable and should be taken into consideration by neonatal practitioners, who should continue to individualize therapy for their patients on a daily basis.

We believe our base case results underestimate the potential NMB associated with transition to calculator-based management of newborns exposed to maternal intrapartum fever. Specifically, we were unable to include other potential cost savings associated with more judicious management, for which incidence and/or cost data are not available. These include reductions in unnecessary laboratory testing, clinical monitoring, and other patient harms, and less well-defined adverse consequences related to delay in initiation of breast-feeding, maternal peripartum depression, and changes in the gut microbiome from broad spectrum antibiotic use [48, 49]. We believe our base-case analysis is clinically justified, given the available data for each of the model parameters. Further, our probabilistic sensitivity analysis provides contextual information on the uncertainty of each parameter to generate a prediction of model outcomes based on the assumed distribution for each.

We acknowledge certain limitations of our analysis. First, because there are scant data on differential downstream clinical risks between the compared groups, no data on long-term negative outcomes to distinguish between infants with culture-negative and culture-positive sepsis, and age-specific limitations in HCUP data for case identification, we combined neonates with confirmed bacteremia and those with clinical sepsis into one group in our base model. We appreciate that in some centers these infants may not be treated similarly and may not have the same downstream risks. However, from a practical clinical perspective, the actual treatment course of a large percentage of septic, non-bacteremic infants does not usually depend on culture results in the absence of specific stewardship activities [6, 50–52]. Importantly, the HCUP data we used to generate LOS and cost figures are a nationally representative sampling of different management approaches for such newborns. Nonetheless, our secondary analysis, which imputed downstream outcomes based on ranges reported in the literature to define the potential extremes, revealed a persistent net benefit per infant in favor of the calculator-based strategy, with a likelihood of 57.4–74.1% in the PSA.

Second, administrative data are variably robust [53], and obtaining precise costs and probabilities for each health state was not always possible. For example, only limited historical data support our assumption that 48 h of empiric antibiotics might prevent subsequent sepsis and/or culture-positive disease among initially asymptomatic and culture-negative newborns [32, 33]. Our sensitivity analyses addressed the uncertainty regarding this and other model parameters. Third, our model did not include other strategies to lessen antibiotic use such as other stewardship interventions, biomarkers, and molecular microbiologic diagnostics [6, 50, 54, 55]. Finally, we could not model infant outcomes according to maternal diagnosis (fever due to a non-infectious cause) or type and duration of intrapartum chemoprophylaxis, due to inadequate clinical data. Our model, therefore, used maternal fever regardless of etiology, as this is the most commonly encountered clinical scenario, and it circumvents the additional uncertainty related to obstetrical practice variation in maternal diagnosis [6, 8, 9].

Our model provides compelling first evidence that a calculator-based management approach—specifically, the use of a validated EOS calculator, in conjunction with clinical evaluation—for neonates exposed to intrapartum fever provides NMB to society. Probabilistic sensitivity analysis suggests that this management strategy has 60% likelihood of resulting in net societal benefit, compared to the CDC/AAP consensus guidelines. At the highest levels of adoption, the calculator-based approach could yield US$510 million in aggregate value to society, and likely more, had

we been able to include other benefits of reduced antibiotic treatment. The robustness of the NMB, combined with consideration of the general benefits of de-escalating care for newborns deemed at lower risk of sepsis, presents useful data for clinicians and other relevant stakeholders in their decision-making regarding neonatal sepsis management.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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