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Antibiotic Stewardship in Premature Infants: A Systematic Review

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Keywords
Antibiotic stewardship · Premature infant · Antibiotic resistance

Abstract
Introduction: Antibiotic treatment in premature infants is often empirically prescribed, and practice varies widely among otherwise comparable neonatal intensive care units. Unnecessary and prolonged antibiotic treatment is documented in numerous studies. Recent research shows serious side effects and suggests long-term adverse health effects in prematurely born infants exposed to antibiotics in early life. One preventive measure to reduce unnecessary antibiotic exposure is implementation of antibiotic stewardship programs. Our objective was to review the literature on implemented antibiotic stewardship programs including premature infants with gestational age ≤34 weeks. ***Methods:*** Six academic databases (PubMed [Medline], McMaster PLUS, Cochrane Database of Systematic Reviews, UpToDate, Cochrane Central Register of Controlled Trials, and National Institute for Health and Care Excellence) were systematically searched. PRISMA guidelines were applied. ***Results:*** The search retrieved 1,212 titles of which 12 fitted inclusion criteria (11 observational studies and 1 randomized clinical trial). Included articles were critically appraised. We grouped the articles according to common area of implemented stewardship actions: (1) focus on reducing initiation of antibiotic therapy, (2) focus on shortening duration of antibiotic therapy, (3) various organizational stewardship implementations. The heterogeneity of cohort composition, of implemented actions and of outcome measures made meta-analysis inappropriate. We provide an overview of the reduction in antibiotic use achieved. ***Conclusion:*** Antibiotic stewardship programs can be effective for premature newborns especially when multifactorial and tailored to this population, focusing on reducing initiation or on shortening the duration of antibiotic therapy. Programs without specific measures were less effective.

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Introduction

Treatment and survival of newborn infants, in particular the premature, often rely on effective antibiotics. Infections are leading causes of morbidity in infancy, contributing to 15% of neonatal deaths worldwide (2017) [1]. Incidence and mortality rates of early-onset sepsis (EOS) are inversely proportional to gestational age (GA) and birth weight [2]. Early neonatal sepsis is often defined by positive microbial cultures from blood or cerebrospinal fluid (obtained within 72 h after birth, and late-onset sepsis after 72 h), in patients with signs or symptoms of systemic infection [2, 3]. Blood cultures are, however, often falsely negative due to difficulties in obtaining sufficient volume, low bacteremia levels, and intrapartum antibiotics [4]. Also, results are not ready before necessary decision on initiation of antibiotics. As laboratory tests may be unspecific and delayed, and clinical signs can be prone to subjective interpretation, risk assessment is often used, with a low threshold for starting empiric antibiotic therapy [2].

Uncertain clinical symptoms and signs, potential disastrous outcome in case of delayed start of antibiotic treatment, and reluctance to withdraw initiated treatment often result in overuse of antibiotics in the neonatal intensive care unit (NICU). In premature infants, antibiotic treatment for >5 days in infants with negative blood cultures is associated with increased risk of necrotizing enterocolitis, bronchopulmonary dysplasia, invasive fungal infections, retinopathy, periventricular white matter damage, and death [5–8]. In addition, antibiotic disruption of the developing microbiome may carry lasting consequences reflected as dysbiosis and increased carriage of antibiotic resistance genes and multidrug resistant organisms [9, 10].

An antibiotic stewardship program (ASP) is defined as "ongoing efforts by a health care organization to optimize antimicrobial use among hospitalized patients in order to improve patient outcomes, ensure cost-effective therapy, and reduce adverse sequelae of antimicrobial use (including antimicrobial resistance)" [11]. Battles against drug-resistant organisms are becoming increasingly challenging and implementation of ASPs is rightfully increasing [12, 13]. For premature infants, the main focus of ASPs entails reducing empiric antibiotics after birth and restricting duration of antibiotic therapy in low risk situations. Additional focus areas include antibiotics pre- and intrapartum, drug selection, dosage, and more [2, 14, 15]. In addition to ASPs, infection prevention and control actions (from hand hygiene, visitor limitations, sterile equipment, and vaccination of health care workers, to interventions related to infrastructure, number of health care workers, and special isolation actions) result in lower incidence of healthcare-related infections and thus lower antibiotic prescription rates [16]. ASPs implemented alongside infection prevention and control are more successful than when implemented alone [17].

The risk-based approach with low threshold is often used for starting antibiotics right after birth, an approach that has successfully lowered EOS incidence but increased number of noninfected infants exposed to antibiotics [4, 18]. Such empiric therapy is often extended to 5 to 7 days even in the absence of positive blood cultures [19]. In a recent study, Flannery et al. [20] demonstrated that the majority of infants <1,500 g from nearly 300 US hospitals were treated with antibiotics in their first days of life, and proximately 1/3 received >5 days of antibiotic treatment. There were major differences between hospitals that could not be explained solely by medical reasons. In the period from 2015 to 2018 >50% of infants born at GA <32 weeks received intravenous antibiotics within the first 14 days of life [21]. Median treatment duration (interquartile range) was 8 (7–10) and 6 (5–7) days for culture-positive and culture-negative EOS, respectively, in the period from 2009 to 2011, and there was great interhospital variation (Norwegian Neonatal Network database) [21].

Antibiotics are essential drugs and their use should be expected to remain high in premature infants, but unnecessary antibiotic exposure must be minimized due to substantial risks of adverse effects [22]. This review aims to summarize available knowledge on ASPs implemented for infants born before 34 weeks GA.

Methods

This systematic review was performed using all applicable items from the PRISMA guidelines (see online suppl. file 1; see www.karger.com/doi/10.1159/000511710 for all online suppl. material).

We performed a search on July 9, 2019, in 6 academic databases. Additional 10 articles were obtained from reference lists. Full search terms and search strategy are provided (online suppl. file 2). A second search performed on December 5, 2019, revealed no additional studies. No previous systematic review of ASPs in premature infants was identified.

We retrieved 1,212 titles, and no duplicates were found. Three authors (P.R., O.D.S., and U.R.D.) screened the titles and abstracts of all (1,212) articles were identified through the search. Comments and guidelines were excluded. We included articles that incorporated any premature infants born ≤34 weeks GA. Infants with extremely low birth weight (<1,000 g) and very low birth weight (<1,500 g) were also regarded as born ≤34 weeks GA where

Table 1. Included studies

Source	Location	Infants, *n*	Gestational age of participants[a]	Study type, ASP details	Main measure of outcome	Relevant findings	Area of actions[b]
Astorga et al. [24]	Wisconsin, USA Level 3 NICU	1,203 564 pre-ASP 639 post-ASP	GA <34 weeks 143 (25.4%) pre-ASP 152 (23.8%) post-ASP	Retrospective (pre and post) cohort observational study Automatic 48-h electronic stop on all parenteral antibiotics	DOT/1,000 patient-days	Total doses of antibiotics per patient decreased by 35% ($p < 0.0001$). Total antibiotic doses per patient-day decreased by 25% ($p < 0.0001$)	2
Bhat et al. [25]	Alabama, USA	NICU with 950 admissions per year, 45% of which have GA <34 weeks	GA of all included infants ranged from 25 to <34 weeks	Retrospective evaluation of antibiotic consumption followed by prospective evaluation of quality improvement interventions Main focus areas were decreasing initiation and duration of exposure to antibiotics among preterm infants with suspected sepsis, minimizing exposure to broad-spectrum antibiotics	DOT/1,000 patient-days	A 10.6% reduction of all antibiotic utilization rates from 154.8 to 138.4 DOT/1,000 patient-days ($p < 0.005$). A decrease in empiric antibiotic use from 112.3 to 86.8 DOT/1,000 patient-days ($p < 0.005$)	1/2/3
Cantey et al. [19]	Texas, USA Level 3 NICU	2,502 1,607 pre-ASP 895 post-ASP	GA <34 weeks 319 (20%) pre-ASP 177 (20%) post-ASP	Observational study 48-h automatic stop for empiric antibiotic therapy. Limited treatment duration of culture-negative sepsis and pneumonia to 5 days	DOT/1,000 patient-days	A 27% decrease in antibiotic use ($p < 0.0001$)	2
Jinka et al. [26]	Andhra Pradesh, India	2,452 1,176 pre-ASP 1,276 post-ASP	VLBW 106 (9%) pre-ASP 74 (6%) post-ASP No GA data	Retrospective interrupted time-series study A new protocol for empiric therapy of neonatal sepsis based on review of blood culture susceptibility data Limitations: no individual patient data	DDD/100 patient-days	A nonsignificant reduction of total antibiotic consumption (from 14.47 to 11.47 DDD/100 patient-days, $p = 0.57$). However, the proportion of babies on antibiotics decreased significantly (58% [$n = 681$] versus 46% [$n = 584$]; $p < 0.001$). Use of first-line agents significantly increased ($p < 0.001$) and use of third generation cephalosporins decreased significantly ($p < 0.001$)	3
Kitano et al. [27]	Nara, Japan Level 3 NICU	1,107 913 pre-ASP 194 post-ASP	VLBW 95 (10.4%) pre-ASP 20 (10.3%) post-ASP Average GA 36 weeks	Retrospective (pre and post) cohort observational study Implemented a protocol of antimicrobial treatment at NICU: new start and stop criteria for antibiotic therapy, weekend report of blood culture results, stopping ordering antimicrobials for the next day	DOT/1,000 patient-days	After ASP implementation, DOT/1,000 patient-days decreased 76.2% ($p < 0.001$), as did the percentage of neonates receiving any antibiotic therapy (55.3 vs. 20.6%, $p < 0.001$) and the percentage of neonates receiving prolonged therapy (and 65.0 vs. 32.5%, $p < 0.001$)	1/2/3
Lu et al. [28]	Shanghai, China Level 3–4 NICU	13,540 7,754 pre-ASP 5,786 post-ASP	GA <34 weeks 1,709 (22%) pre-ASP 1,330 (23%) post-ASP	Prospective interrupted time-series study SMAP[c] implementation, baseline and post-intervention assessments. SMAP consisted of antibiotic restrictions, reviews of electronic medical records, SNAPPE-II[d] assessments, and a 48-h automatic stop order on empiric antibiotic therapy	DOT/1,000 patient-days	33% decrease in DOT/1,000 patient-days ($p = 0.0001$) A significant decrease in LOS ($p = 0.03$), in percentage of infants with discontinued treatment after 48 h ($p = 0.0001$) and in percentage of infants with negative blood cultures treated for ≥5 days ($p = 0.02$)	2/3

Table 1 (continued)

Source	Location	Infants, *n*	Gestational age of participants[a]	Study type, ASP details	Main measure of outcome	Relevant findings	Area of actions[b]
McCarthy et al. [29]	Cork, Ireland level 3 NICU	312 124 pre-ASP 82 post-first intervention 106 post-second intervention	GA <32 weeks 10 (8%) pre-ASP 19 (23%) post-first intervention 12 (11%) post-second intervention	Prospective audit with 2 reaudit periods A prospective audit was first performed, followed by implementation of electronic prescribing and staff education. Two subsequent audits were performed, with a 36-h automatic stop of antibiotic therapy implemented after the second reaudit	DOT/1,000 patient-days and infants receiving prolonged antibiotic therapy	They achieved a 27% decrease in DOT/1,000 patient-days. In addition, there was also a significant decrease of prolonged (>36 h) antibiotic therapy in negative sepsis evaluations ($p = 0.0040$) and a decreased in prolonged (>5 days) antibiotic treatment in culture-negative sepsis ($p = 0.0009$)	2/3
Nitsch-Osuch et al. [30]	Wroclaw, Poland	418 208 pre-ASP 210 post-ASP	53% pre-ASP and 51% post-ASP diagnosis of hospitalized infants were prematurity and intrauterine infections No other GA or BW data	Retrospective (pre- and post) cohort observational study Implementation of hospital antibiotic policy by the hospital infection control team (reassigning first-, second-, and third-line antibiotics) Limitations: no individual patient data	DDD/100 patient-days	Slight increase in total antibiotic consumption, but an improved profile of antibiotic consumption	3
Nzegwu et al. [31]	Massachusetts, USA level 4 NICU	4,551 1,204 pre-ASP 3,347 post-ASP	ELBW 118 (9.8%) pre-ASP 282 (8.4%) post-ASP Average GA 35.4 weeks pre-ASP 35.5 weeks post-ASP	Retrospective interrupted time-series study New recommendations for evaluation and treatment of neonatal sepsis. Prescriber audit and feedback	DOT/1,000 patient-day	Significant decline in LOS evaluation and prescription events post-ASP ($p < 0.001$). This was not reflected in the total antibiotic utilization, as only a slight decrease in DOT/1,000 patient-days ($p = 0.699$) was observed	3
Tagare et al. (2010) [32]	Pune, India	140 71 control group 69 intervention group	VLBW: 53 (38%) 26 (37%) in control group 27 (39%) in intervention group All participants GA ≤36 weeks	RCT of routine antibiotic treatment Premature infants (with no other risk factors) were assigned to either control (no antibiotic therapy) or intervention group (5 days of intravenous antibiotic treatment)	Incidence of sepsis	Comparable incidence of sepsis in both groups (25.4 and 31.9% for control and intervention group, respectively), also in VLBW infants (42.3 and 59.3% for control and intervention group, respectively)	1
Ting et al. [33]	Vancouver, Canada level 3–4 NICU	2,670 2,003 pre-ASP 667 post-ASP	VLBW 569 (28%) pre-ASP 154 (23%) post-ASP No GA data	Retrospective audit and post-ASP reaudit A retrospective audit focused on prolonged (>3 days) antibiotic prescriptions and evaluation according to the 12 steps of CDC. Audit was repeated 12 months after ASP implementation. New approach to LOS management in order to reduce unnecessary prolonged antibiotic exposure New diagnostic tools (MALDI-TOF) for early identification of organisms, education of staff. There was no change in the protocols for empiric antibiotic therapy (except restriction of linezolid)	Inappropriate antibiotic-days/1,000 patient-days	Inappropriate antibiotic-days/1,000 patient-days decreased from 3.56 to 1.73 (RR, 0·49 [95% CI: 0·33–0·71]), but no improvement was seen in the VLBW group	2/3

Table 1 (continued)

Source	Location	Infants, *n*	Gestational age of participants[a]	Study type, ASP details	Main measure of outcome	Relevant findings	Area of actions[b]
Tolia et al. [34]	Texas, USA	674 313 pre-ASP 361 post-ASP	All infants had GA <28 weeks and VLWB	Retrospective (pre and post) cohort study Automatic 48-h electronic stop and education of health staff Limitation: antibiotic use was recorder only for the first 7 DOL	DOT/1,000 patient-days and percentage of infants receiving prolonged therapy	28% decrease in DOT/1,000 patient-days ($p < 0.001$) Decrease in percentage of infants with antibiotics >48 h ($p < 0.001$)	2

NICU, neonatal intensive care unit; ASP, antibiotic stewardship program; CDC, Center for Disease Control and Prevention; DOT, days of therapy; DOL, days of life; DDD, defined daily dose; ELBW, extremely low birth weight; EOS, early-onset sepsis; GA, gestational age; LBW, low birth weight; LOS, late-onset sepsis; MALDI-TOF, matrix-assisted laser desorption/ionization-time of flight; VLBW, very low birth weight; RCT, randomized clinical trial. [a] Since not all articles reported the distribution of gestational age, we also included infants with VLBW, to be ≤34 weeks GA. This was deducted from growth charts of premature infants, as we expect infants with BW of 1,500 g to have GA, between 27 and 34 weeks (3–97th percentile) [23]. Similarly, infants with ELBW, were also regarded to be ≤34 weeks GA. [b] Grouping according to type of ASP, actions used in the studies, explained in Results. Group 1: focus on reducing initiation of antibiotic treatment. Group 2: focus on discontinuation of antibiotic treatment. Group 3: various organizational ASP, actions. [c] SMAP, smart use of antibiotics program. [d] SNAPPE II, Scores for Neonatal Acute Physiology with Perinatal Extension – II assessment.

GA of included infants was not transparent from the article [23]. We included articles that compared use of antibiotics before and after ASP implementation. We excluded articles where antibiotic stewardship actions were directed toward specific microorganisms and articles that reported the current state of antibiotic consumption and possibilities for ASP but lacked results of ASP actions. Papers that targeted antibiotic usage in a more specific group of infants only (e.g., surgical prophylaxis) were also excluded. In total, 29 full-text articles were retrieved for these criteria, or required more information than was provided in the abstract for an informed decision. Two investigators (P.R. and K.H.) independently assessed the full-text articles. A total of 12 articles were included in the review (Table 1; Fig. 1). Seventeen studies were excluded for reasons described in Table 2. Study quality and risk of bias were assessed by 2 investigators (P.R. and K.H.), using Newcastle-Ottawa quality assessment scale for the 11 cohort studies and Jadad scale for the randomized clinical trial (RCT) (online suppl. 3, 4).

Results

The 12 selected articles varied greatly in their study population, interventions, and outcome measures (as detailed in Table 1). To summarize and compare their findings we identified (1) common areas of action (Fig. 2) and (2) common units of measurement for reporting results (Fig. 3, 4). Five articles included more than one area of action.

Common Areas of Action (3 Groups)

Group 1: three out of the 12 studies focused on *restricting initiation of antibiotics*. Tagare et al. [32] performed a RCT to evaluate the protective effect of empiric antibiotic coverage in premature infants in low-risk situations. Infants with no other risk for infections were randomized to the control or to the intervention group with 5 days of antibiotic prophylaxis. Bhat et al. [25] encouraged empirical antibiotic use only in the presence of perinatal risk factors for EOS or in infants with postnatal clinical illness suggestive of evolving sepsis. Kitano et al. [27] implemented comprehensive criteria for initiation of antibiotic treatment, based on maternal chorioamnionitis, infant's clinical presentation, and laboratory values combined. Both Kitano et al. and Bhat et al. [25, 27] also applied interventions from the 2 other areas of action.

Group 2: eight out of the 12 studies implemented actions toward *reducing duration of antibiotics*. Astorga et al. [24] implemented a 48-h automatic stop on empiric antibiotics initiated in infants at risk for infection without other changes to their practice. The same was done by Cantey et al. [19], additionally limiting treatment duration of culture-negative sepsis and pneumonia to 5 days.

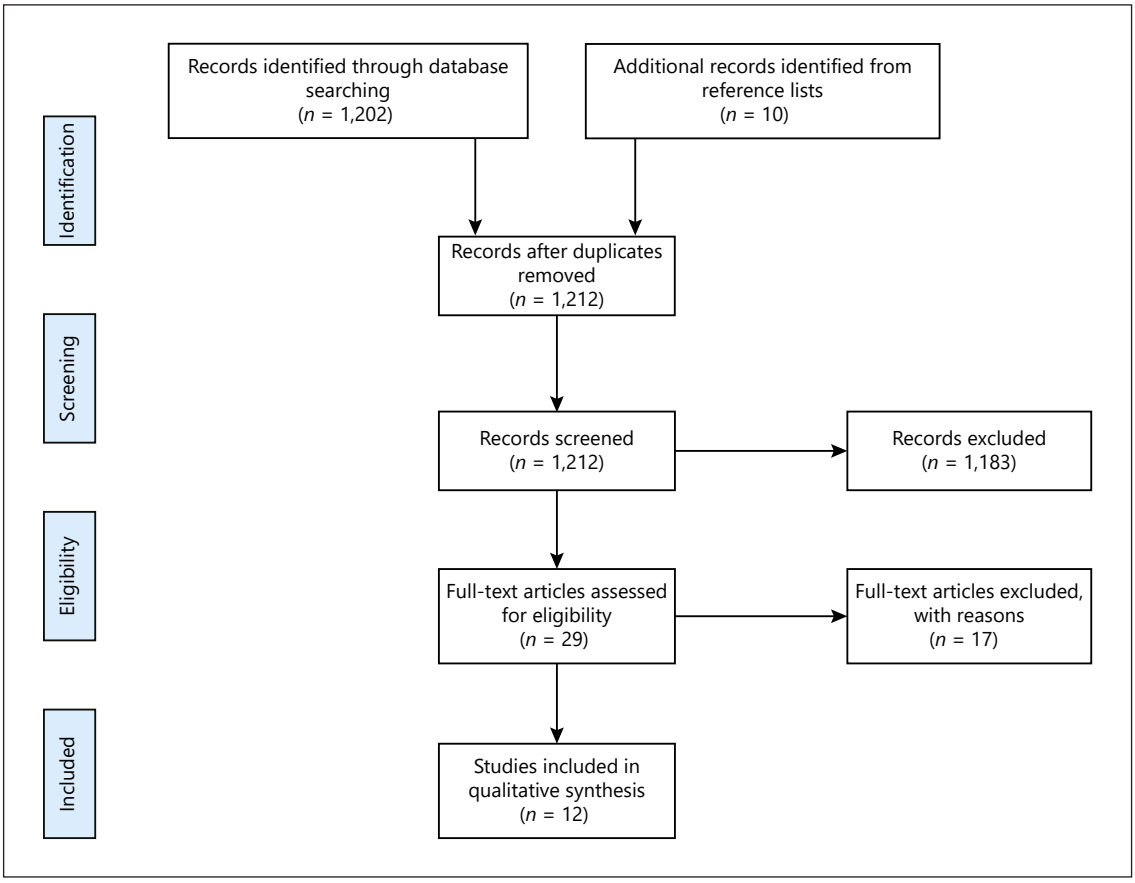

Fig. 1. Study selection process.

Tolia et al. and Lu et al. [28, 34] implemented an automatic stop order at 48 h in addition to other educational and organizational ASP actions, respectively. McCarthy et al. [29] specifically targeted prolonged antibiotic courses in their second of 2 intervention periods, implementing an automatic stop after 36 h in asymptomatic infants with 2 negative CRP and negative blood culture. Similarly, 3 more studies encouraged discontinuation of antibiotic treatment within 36–48 h in infants with negative cultures and no clinical or laboratory suspicion of sepsis [25, 27, 33].

Group 3: eight out of the 12 studies implemented *various organizational ASP actions*. Jinka et al. and Nitsch-Osuch et al. [26, 30] implemented a protocol for empiric treatment and for antibiotic prescriptions, respectively. They provided no individual level data. Nzegwu et al. [31] evaluated the implementation of new guidelines for neonatal infection assessment and unit-wide ASP education, focusing especially on management of late-onset sepsis, without any specific actions (such as an automatic stop order) taken. The remaining 5 studies used also actions from groups 1 or 2, described above. Lu et al. [28] reassigned first, second, and third line antibiotic to restrict consumption of broad-spectrum antibiotics. They reviewed electronic records of all antibiotic use in the NICU. Health personnel was informed and trained for the ASP interventions after the baseline period. McCarthy et al. [29] also focused on educational interventions based on monitored antibiotic prescribing data. Ting et al. [33] implemented 3 of the 12-steps program from Centers for Disease Control and Prevention, adjusted for the NICU population: "target the pathogen," "practice antimicrobial control," and "know when to say no." After performing a retrospective audit for prolonged (>3 days) antibiotic prescriptions, their multidisciplinary ASP NICU team defined appropriate uses of antibiotics in different clinical situations, performed staff education, and implemented a new diagnostic tool to allow for earlier

Table 2. Full-text articles excluded

Article	Short description	Reason for exclusion
Achten et al. [39]	Implemented sepsis calculator to reduce empiric antibiotics for suspected EOS in a cohort GA ≥35 weeks with either elevated maternal EOS risk or/and possible EOS based on clinic presentation within 72 h. They observed a significant reduction in empiric antibiotic therapy (from 4.8 to 2.7%, $p < 0.001$)	Excluded because their cohort included no infants with GA ≤34 weeks
Alturk et al. [50]	Investigated factors responsible for prolonged antibiotic therapy in premature infants born <29 weeks GA.	Excluded because it did not explore if influencing these factors in real settings would have any beneficial effect
Ariffin et al. [51]	Assessed the influence of a ward tailored (NICU) antibiotic policy by comparing causative agents of nosocomial bloodstream infections with those found in an adult intensive care unit	Excluded as it focused on microorganisms found in NICU and not on the antibiotic consumption in infants
Bertini et al. [14]	Evaluated an indirect action to reduce consumption of antibiotics by using special coated catheters for prevention of CRBSI. Even though they observed a significant reduction in CRBSI ($p = 0.005$), there was no difference in consumption of antibiotic prophylaxis. They did not report how lower rates of infections influenced antibiotic consumption at the NICU.	Excluded because the primary outcomes were not directed toward lowering consumption of antibiotics but rather preventing infections
De Man et al. [52]	Implemented an antibiotic policy and reported its effect as emergence of resistant bacteria. It showed that policies regarding empiric antibiotic therapy influence the control of antimicrobial resistance	Excluded because it reported no data on how the policy influenced antibiotic consumption for infants
Di Pentima et al. [53]	Described the impact of the implementation of an ASP on prescription errors for hospitalized children	Excluded because it did not report the effect of ASP on use of antibiotics in infants
Garner et al. [54]	Evaluated the effectiveness of an interactive computerized order set to prevent prescription errors in neonatal LOS	Excluded because it did not evaluate the influence of this program on initiation, duration, or total use of antibiotic therapy
Ho et al. [55]	Observed the adherence of ASP according to CDC recommendations	Excluded because it did not report data on antibiotic consumption before/after implementation of the program
Kuzniewicz et al. [38]	Created a predictive model of neonatal EOS risk, including a study cohort of 204,485 infants their work has been an important milestone in reducing unnecessary exposure in premature infants	Excluded because the population had a GA ≥35 weeks
Malcolmson et al. [56]	Investigated the combined impact of MALDI-TOF technology and an ASP in pediatric patients with bloodstream infections	Excluded because it did not report changes in initiation or duration of antibiotic treatment in infants
Money et al. [57]	Hypothetical retrospective study to evaluate if the use of EOS calculator (developed by Kaiser Permanente ref) would safely reduce antibiotic use in well-appearing term infants born to mothers with chorioamnionitis. This hypothetical study showed that management according to the EOS calculator would reduce antibiotic use in infants ($p = 0.0001$) and average length of therapy ($p = 0.0001$)	Excluded because it was a theoretical study, and the cohort was composed of term infants
O'Leary et al. [58]	Described a surveillance strategy to monitor antibiotic use and improve antibiotic stewardship in neonates	Excluded because it had no data on antibiotic use before and after implementation of the strategy
Patel and Saiman [47]	Observed the adherence of ASP according to CDC recommendations	Excluded because it did not report data on antibiotic consumption before/after implementation of the program
Steinmann et al. [46]	Assessed impact of empowering leadership style on ASP in a NICU/PICU over 3 years. They reported a significant decline in antibiotic days per 1,000 patient-days	Excluded because it was targeted toward all pediatric patients and did not report any data separately for neonates
Stocker et al. [59]	Evaluated a 3 months surveillance strategy for antibiotic consumption according to the CDC 12-step campaign in a pediatric intensive care unit. It reported increased percentage of appropriate empiric therapy courses ($p < 0.001$), increased correct targeting of pathogen ($p = 0.21$), and reduced duration of therapy ($p = 0.05$)	Excluded because it focused on all pediatric patients without reporting any data separately for neonates

Table 2 (continued)

Article	Short description	Reason for exclusion
Toltzis et al. [60]	Focused on the influence of antibiotic rotations in NICU (monthly rotation of gentamicin, piperacillin-tazobactam, and ceftazidime) on colonization with resistant microorganism in the infants	Excluded because it focused on microorganisms, and did not report patent-level data on possible changes in initiation or duration of antibiotic treatment
Walker et al. [15]	Showed results of ASP in neonatal surgical patients. This is a specific group of infants, mostly not premature, in specific situations (antibiotic prophylaxis at surgical procedures)	Excluded because it targeted a specific group of infants (neonates with congenital surgical conditions) with average (IQR) GA 37 (35–39) weeks

EOS, early-onset sepsis; GA, gestational age; ASP, antibiotic stewardship program; NICU, neonatal intensive care unit; CRBSI, catheter-related bloodstream infections; LOS, late-onset sepsis; CDC, Center for Disease Control and Prevention; MALDI-TOF, matrix-assisted laser desorption/ionization-time of flight.

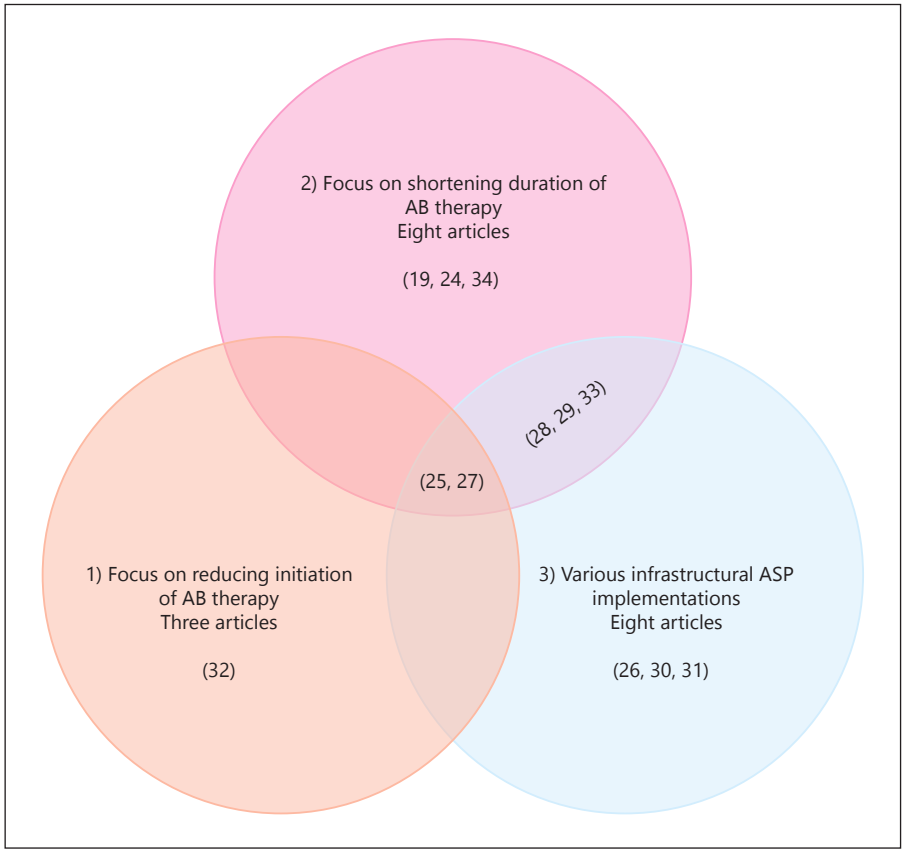

Fig. 2. Antibiotic stewardship interventions groups according to common areas of action. (1) Focus on initiation of antibiotic therapy. (2) Focus on shortening duration of antibiotic therapy. (3) Various organizational ASP implementations. There is overlap in the studies implementing various actions. The first 2 areas used actions tailored to NICU patients, while actions from the third area are less specific and could be adapted to health settings in general. ASP, antibiotic stewardship program; NICU, neonatal intensive care unit.

identification of organisms. Kitano et al. and Bhat et al. [25, 27] used action from all 3 areas. Bhat et al. [25] aimed to minimize exposure to broad-spectrum antibiotics. A multidisciplinary team created guidelines for management of sepsis, including an algorithm to recognize coagulase-negative blood culture contamination. All staff underwent multiple educational and discussion sessions. PCR became routinely used to rapidly identify pathogens from positive blood cultures or cerebrospinal fluid samples [25]. Kitano et al. discussed cases of noncompliance collegiately on a daily basis and made blood culture results available also on weekends and holidays [27].

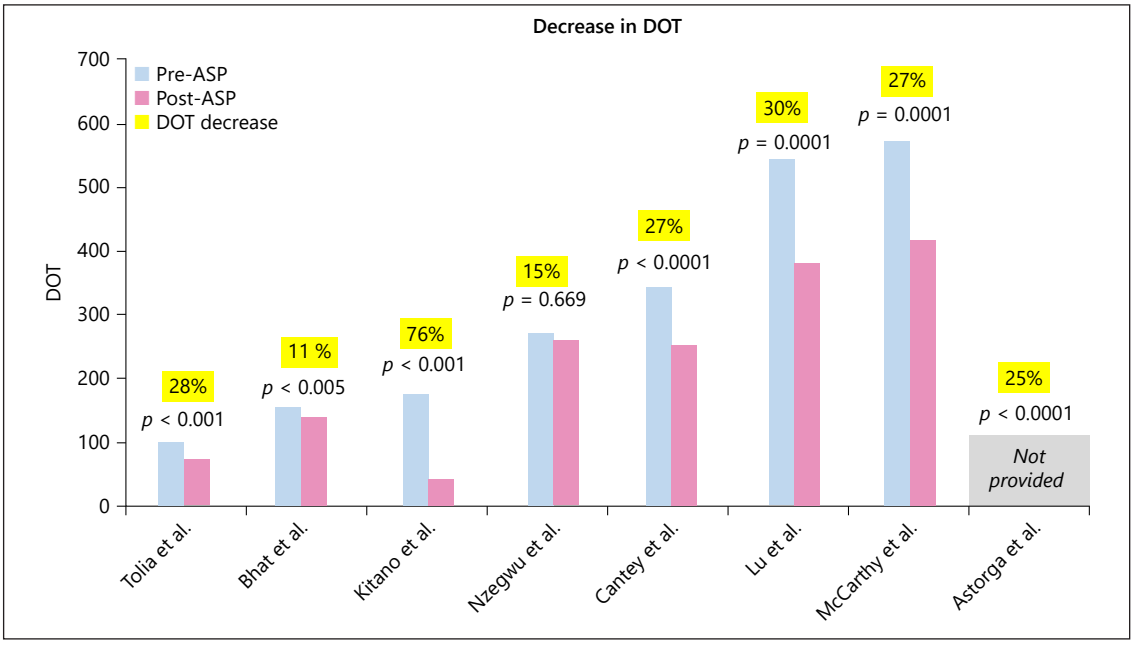

Fig. 3. DOT/1,000 patient-days. Starting with the lowest baseline antibiotic consumption, Tolia et al. [34] achieved a significant reduction from 99.5 to 71.7 DOT patient-days. Bhat et al. [25] achieved reduction of all antibiotic utilization rates from 154.8 to 138.4 DOT. Kitano et al. [27] achieved a decrease from 175.1 to 41.6 DOT. Only one study (Nzegwu et al. [31]) did not find a significant decrease of total antibiotic consumption. Cantey et al. achieved a reduction from 343.2 to 252.2 DOT [19]. Lu et al. [28] achieved a decrease from 543 to 380 DOT. McCarthy et al. [29] reduced antibiotic use from 572 to 417 DOT after second intervention. Astorga et al. [24] was able to achieve a significant 25% decrease in antibiotic consumption. DOT, days of therapy; ASP, antibiotic stewardship program.

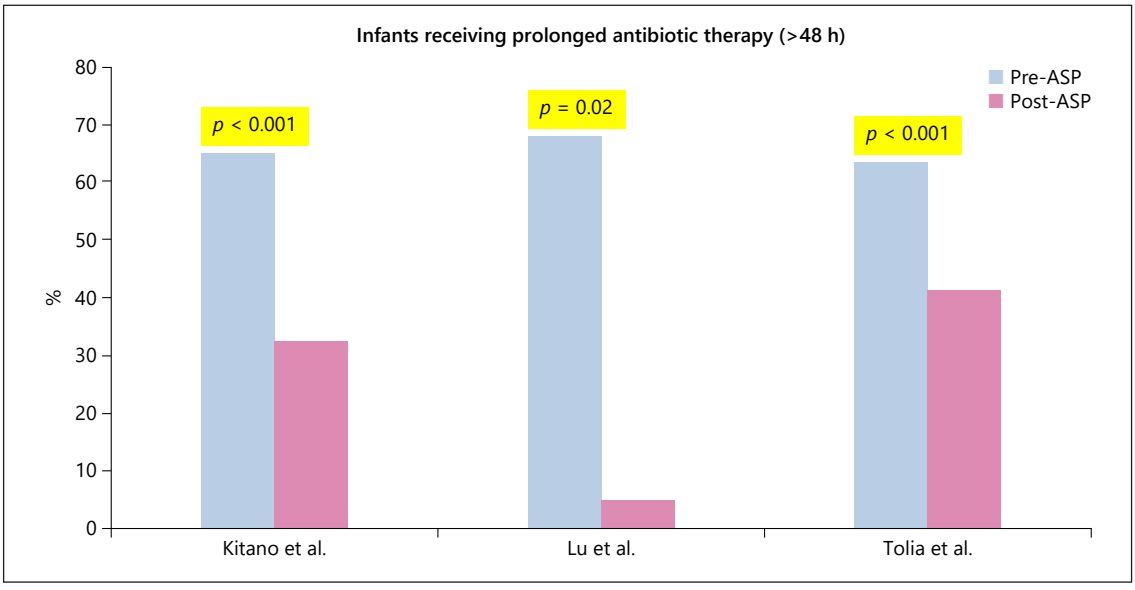

Fig. 4. Percentage of infants receiving prolonged (>48 h) antibiotic therapy. Kitano et al. [27] achieved a reduction of prolonged antimicrobial treatments from 65 to 32.5%. Lu et al. [28] had an increase in percentage of discontinued antibiotic courses ≤48 h from 32 to 95%. Tolia et al. [34] lowered percentage of infants with >48 h of antibiotic exposure from 63.4 to 41.3%.

Antibiotic Stewardship Articles Grouped according to Common Units of Measurement for Reporting Results

Most commonly used units of measurement describing success of ASP in reducing amount of antibiotic consumption were days of therapy/1,000 patient-days (DOT) and defined daily dose/100 patient-days (DDD) [35]. DOT represents the actual number of doses received by the patients and is preferred in pediatrics as dosage is weight- and age-adjusted. DDD gives information of the volume of antibiotic used by a unit. It is easy to obtain (pharmaceutical records) but lacks individual level data.

Papers listed under one of the first two areas of action used individual patient data and mostly expressed their results as DOT, or percentages of infants receiving antibiotic treatment before and after ASP implementation. Two papers using actions from the third area reported their result as DDD.

Days of Therapy/1,000 Patient-Days

Eight out of the 12 studies expressed their result in DOT (Fig. 3) [19, 24, 25, 27–29, 31, 34]. All but one study [31] found significant decrease in total antibiotic consumption.

Additionally, Ting et al. [33] looked at the proportion of infants with negative blood cultures receiving prolonged antibiotic therapy (>3 days) and found a nonsignificant change in inappropriate antibiotic-days/1,000 DOT courses of therapy with meropenem, cefotaxim, and vancomycin from 1.89 to 1.96 (rate ratio [RR], 1.04 [0.70–1.52]), 3.56 to 1.73 (RR, 0.49 [0.33–0.71]), and 2.70 to 1.01 (RR, 0.37 [0.22–0.60]), respectively.

Defined Daily Dose/100 Patient-Days

Two out of the 12 studies used general oriented approaches for their ASP and expressed results as DDD [26, 30]. Jinka et al. [26] observed a nonsignificant reduction of DDD of antibiotic (from 14.47 to 11.47, $p = 0.57$), but the proportion of babies on antibiotics decreased significantly ($p < 0.001$). They also achieved a significant increase in consumption of first-line antibiotics ($p < 0.001$) and a significant decrease in third generation cephalosporins ($p = 0.002$). The effect of the ASP described by Nitsch-Osuch et al. [30] resulted in a slight increase of DDD (from 28.9 to 30.8). However, they also observed a positively changed antibiotic consumption profile.

Percentage of Infants Starting or Receiving Prolonged Antibiotic Therapy

Kitano et al. [27] achieved a significant reduction from 55.3 to 20.6% ($p < 0.001$) infants receiving any antibiotic treatment. Three studies showed decrease in percentage of infants receiving prolonged (>48 h) antibiotic therapy (Fig. 4) [27, 28, 34]. One also showed a decrease in infants with culture-negative sepsis receiving ≥5 days of antibiotics (from 66 baseline to 33% post-intervention) [28].

The only randomized control trial, performed by Tagare et al. [32], did not report results in units that describe amounts of used antibiotics, but they found no increase in sepsis incidence or mortality in low-risk infants not receiving empiric antibiotics treatment compared to infants receiving 5 days of prophylactic antibiotics (71 infants, sepsis incidence 25.4%, mortality 2.8% vs. 69 infants, sepsis incidence 31.9%, mortality 2.9%), not even in the subgroup of very low birth weight infants (sepsis incidence 42.3%, mortality 3.8% vs. sepsis incidence 59.3%, mortality 7.4% for control and intervention groups, respectively).

Discussion

Several approaches may reduce unnecessary antibiotic exposure. In this systematic review of infants born ≤34 weeks GA, we identified 12 articles describing different ASPs. Due to great heterogeneity in cohorts, implemented actions, and outcome measures, meta-analysis was considered inappropriate. The selected studies also differ in resources and starting point regarding prescribing antibiotics. When the baseline is "5 days of antibiotics to all premature babies," small efforts are needed for significant improvement. In departments with the most severely ill and fragile neonates and/or where several measures to restrict unnecessary antibiotics have already been implemented, it is harder to see significant positive development [31]. We found reduction in use of antibiotics in studies focusing directly toward reducing initiation or on shortening the duration of antibiotic therapy. Studies focusing solely on general intentions, without specific individual-dependent measures, did not demonstrate the same reduction in consumption. They were, however, able to achieve a reduction in the use of resistance driving broad-specter antibiotics.

There is a general lack of information on ASPs for premature infants, especially those <34 weeks GA. Four of the studies selected in our review included exclusively premature infants (GA <37 weeks) [25, 32–34], of which 2 studies included only infants born at <34 weeks [25, 34]. Other selected studies included <50% infants <34 weeks, and results for different stages of prematurity were not always reported separately (details in Table 1). It is, thus,

not clear if their changes of antibiotic consumption reflect mostly term, late-premature, or more immature infants.

Management of potential sepsis differs between mature and premature infants [2, 36, 37]. There is no online prediction tool (similar to the Kaiser calculator [18, 38, 39]) for infants <34 weeks GA, but published protocols similar to Kitano et al. [27] may be useful. This guidance algorithm, successful in reducing initiation of antibiotic therapy, is based on clinical status of mother and infant, sepsis score of the infant, blood culture results, and time progression of symptoms [27]. "Clinical status" and "progression of symptoms" in premature infants are the more challenging parts of such tools, both for initiation and duration of treatment. Several studies showed that an automatic stop of antibiotics after 36–48 h efficiently decreased unnecessary antibiotic exposure in premature infant. Three studies [24, 28, 34] used this as one of the main or only intervention and found significant reduction in total antibiotic doses on individual levels. Another study implemented automatic stop as their second intervention, after thoroughly revising and troubleshooting their antibiotic prescriptions routines [29] and then significantly reduced antibiotics consumption. One study additionally limited the duration of antibiotic for culture-negative sepsis and pneumonia to 5 days [19]. All studies did, however, require *clinical evaluation*, some as supplement to the stop order, all for continuous evaluation of need to reconsider treatment.

The quality of the clinician's evaluation is dependent on more than skills. Close monitoring and series of physical examinations may reduce unnecessary initiation of antibiotics [40], but sufficient human and material resources are needed. Furthermore, cooperation with obstetricians is essential for providing exact information of the circumstances of preterm birth and thereby evaluation of risk factors. Proximity and communication with laboratories, their efficacy and ability to provide accurate and suitable biochemical tests (e.g., serial procalcitonin), and fast identification of infectious agents and resistance profile, influence the possibility and the timeline of making decisions [41, 42]. This may explain some of the variance in use of antibiotics across different NICUs.

We further compared the decrease in DOT in the different studies with the action areas they included in their ASPs (Fig. 3). Kitano et al. and Bhat et al. [25, 27] combined actions from all 3 areas and reported the highest (76%) and the lowest (10.6%) decrease, respectively. Studies combining 2 of the action areas presented medium decrease (28–30%) [28, 29, 34], while the studies focusing on one action area alone achieved a 27 [19], 25 [24], and 15% [31] decrease in DOT. The 2 studies with the least decrease in DOT had quite low baseline consumption before the reported ASPs. Earlier implemented actions to reduce antibiotic consumption and the differences between the populations (i.e., age and NICU level) are important to consider when evaluating the results (details in Table 1).

Recent research has revealed adverse effect of antibiotic exposure on health of premature infants [5, 43]. Individual adverse outcomes should be emphasized when deciding on initiating and discontinuing antibiotic treatment. Additionally, antibiotic resistance is a fast-increasing global challenge. Antibiotic therapy in early life disturbs the developing microbiome, increases carriage of antibiotic resistance genes, and could contribute to increased antibiotic resistance in the population [44]. The clinician needs to balance the fear of not providing necessary antibiotics to treat infections with the risk of short- and long-term negative effects. Local customized studies (similar to Tagare et al. [32]) may reduce the fear of the clinicians, of overlooking the need of antibiotics resulting in disastrous effects.

Even though ASPs largely target clinical personnel, it is imperative that also leaders acknowledge the clinical challenges, encourage transparency and nonpunitive culture, and endorse these programs [45, 46]. The study by Nzegwu et al. [31] also demonstrates the fruits of joint efforts between health authorities and clinicians. They utilized guidelines for design and implementation of a NICU-specific ASP developed by Patel and Saiman [47] which is based on CDC's Get Smart for Healthcare campaign [48]).

Conclusion

In the reviewed studies, the most successful actions in reducing unnecessary antibiotic exposure in premature infants appeared to be the implementation of multivariable risk assessments and clinical tools developed for decisions on initiation of antibiotic treatment of suspected or potential sepsis, and the use of automatic stop in antibiotic prescriptions. A thorough evaluation of the current state at the NICU also helps identify weak points of antibiotic-prescribing practices and allows for a custom-tailored ASP [29]. In the selected studies, general actions for limiting antibiotic use on the hospital level only were less successful in reducing antibiotic exposure in premature infants but could improve the profile of used antibiotics.

This lead to the presumption that a locally customized, multifactorial, broad approach, most of all with individual patient-focused outcome measures is preferable.

Limitations

There are limited studies regarding ASPs for premature infants. Our search string was constructed to find studies using terms such as drug prescription practices or drug utilization. Studies without these terms have been missed by our search. No reports of adverse outcomes of ASPs are documented. Reviewed studies varied in GA of included infants (as most studies encompassed the entire NICU population), in settings, outcome measures, and in the duration of pre- and post-ASP intervention periods. Some variation in assessed quality of included articles was found (online suppl. 3, 4). The 11 observational articles achieved scores suggesting high quality (7 of more out of 9), while the risk of bias was assessed to be high in the 1 RCT (Jadad score 3 or less). However, the article was not excluded as we did not synthetize any new data, rather summarized and described published findings.

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Statement of Ethics

The paper is exempt for Ethics Committee approval as this is a systematic review using data from published literature and no additional patient data were collected.

Conflict of Interest Statement

A.D. and S.S.M. are employed by the R&D division of Tata Consultancy Services Limited (TCS) and declare no conflict of interest. All other authors have no conflict of interest to declare.

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Author Contributions

F.C.P. and U.R.D. conceived the presented idea. All authors developed the protocol, and P.R., K.H., U.R.D., and O.D.S. performed the literature search. P.R. took the lead in writing the manuscript. All authors provided critical feedback and helped shape the manuscript.

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