Are newer drugs better? An analysis of neonatal pharmacological treatments across generations

Lai, Nai Ming; Veettil, Sajesh K; Chaiyakunapruk, Nathorn; Glasziou, Paul

Published in:
Medical Principles and Practice

DOI:
10.1159/000539729

Medical Principles and Practice

Original Paper

Med Princ Pract 2024;33:471–477
DOI: 10.1159/000539729

Received: March 7, 2024
Accepted: June 4, 2024
Published online: June 10, 2024

Are Newer Drugs Better? An Analysis of Neonatal Pharmacological Treatments across Generations

Nai Ming Lai[a] Sajesh Kalkandi Veettil[b] Nathorn Chaiyakunapruk[c] Paul Glasziou[d]

[a]School of Medicine, Faculty of Health and Medical Sciences, Taylor's University, Subang Jaya, Malaysia; [b]School of Pharmacy, Department of Pharmacy Practice, International Medical University, Kuala Lumpur, Malaysia; [c]Department of Pharmacotherapy, University of Utah College of Pharmacy, Salt Lake City, UT, USA; [d]Institute for Evidence-Based Healthcare, Faculty of Health Sciences & Medicine, Bond University, Gold Coast, QLD, Australia

Highlights of the Study

- We compared the efficacy of newer versus older medications used in neonatal care by analysing network meta-analyses.
- Out of 72 comparisons between a pharmacological intervention and its immediate predecessor, only 3 (4.2%) showed statistically significant superiority in efficacy.
- There is no clear time trend showing newer interventions to be more efficacious than older interventions in neonatal care.

Keywords
Neonates · Pediatrics · Pharmacological interventions · Network meta-analysis

Abstract

Introduction: We evaluated the relative effects of newer versus older medications for neonatal conditions and trends in margin of superiority across generations. ***Materials and Methods:*** We assessed network meta-analyses (NMAs) on neonatal pharmacological interventions identified from MEDLINE, Cochrane, and PROSPERO. Interventions were chronologically arranged based on the earliest study and compared for their effects against placebo or no treatment and their immediate predecessor. We assessed the time trend in effect sizes using the Mann-Kendall test. ***Results:*** From 8,048 retrieved records, 10 neonatal NMAs covering 352 trials and 102,653 participants were included. Compared to placebo, 56/61 (91.8%) interventions showed superiority with 23 (37.7%) statistically significant. Compared to previous generation, 47/72 (65.3%) showed superiority with 3 (4.2%) statistically significant. No significant trends in effect sizes were observed across generations for most conditions ($p = 0.09–1$). ***Conclusions:*** We found no evidence that newer generation medications in neonatal care are consistently more effective than older generation medications.

karger@karger.com
www.karger.com/mpp

Correspondence to:
Nai Ming Lai, lainm@doctors.org.uk

Introduction

Pharmacological interventions are integral in the management of neonates alongside respiratory support, nutrition, fluid and infection control measures [1]. The appropriate use of medications can greatly influence short and long-term outcomes [2]. Neonatology is one of the most active fields in clinical research. However, the conclusiveness of the evidence has decreased over time. In two separate analyses of Cochrane neonatal reviews published in 2006 [3] and 2020 [4], the proportion of conclusive reviews decreased from two-thirds to one-third. Increasing number of available medications combined with decreasing conclusiveness of evidence make it challenging for physicians to determine the best course of treatment [5].

Newer medications are introduced with claims of superiority in one way or another, with few studies that evaluated comparative effectiveness of medications developed across generations. Studies in adults to date have focused on safety and tolerability, as in the case of H_1-antihistamine, antiepileptics, and antidepressants [6–8].

With increasing interventions in neonatal care, robust comparative evidence of all interventions as typically reported in a well-conducted network meta-analysis (NMA) [9] is essential to guide clinical decision-making. To our knowledge, an analysis of the comparative effectiveness of neonatal pharmacological treatment across generations has not been published. In this study, we determined the proportion of newer medications that were more effective than older ones in neonatal care and assessed the time trend in their margins of superiority.

Materials and Methods

This meta-research was registered in PROSPERO (CRD42022333299). We searched MEDLINE (PubMed), Cochrane (CENTRAL) (covering the Cochrane Library, EMBASE, CINAHL, and clinicaltrials.gov, WHO international Clinical Trials Registry platform [ICTRP]), and PROSPERO for published NMAs in September 2022 without language restriction. We used the following keywords: "infant, newborn" [MeSH Terms] OR "newborn*" [Title/Abstract] OR "neonat*" [Title/Abstract] OR "infant*"[Title/Abstract]) AND "meta-analysis"(Publication Type).

We included NMAs that evaluated pharmacological interventions with at least one patient-important outcome. Here we broadly classified pharmacological interventions to include nutritional supplements and probiotics. We selected NMAs because they evaluate multiple interventions contemporaneously and include evidence from direct and indirect comparisons, unlike pairwise meta-analyses, which typically only analyse evidence from direct comparisons [9]. We assessed the following endpoints: (i) proportion of newer interventions that were more efficacious than older interventions, (ii) trend of effect sizes across generations of interventions.

Two authors (N.M.L. and S.K.V.) independently screened and selected articles. Among overlapping NMAs, we selected the most recently published, or one with the largest number of included studies. We extracted the following data into a dedicated spreadsheet: first author, interventions, comparison/s, outcomes, earliest and latest published trials. For each NMA, one representative dichotomous patient-important outcome was selected for analysis, in the following order of priority [10]: mortality, incidence of major morbidities such as BPD/CLD, IVH, PDA or NEC, other clinical endpoint (e.g., treatment failure), length of stay, neurodevelopmental outcomes. We resolved disagreements by discussion leading to a consensus, which was achieved without the need for a referral to the third author (N.C.). We extracted effect sizes (risk ratio (RR) or odds ratio (OR) with 95% confidence interval) of each intervention for the chosen outcome, against placebo/no intervention and against its nearest predecessor with available data. We standardised all outcomes to negative (e.g., survival to mortality or PDA closure to failure of PDA closure) with inversion of corresponding effect sizes where necessary. We arranged each intervention in chronological order according to the earliest study. For interventions with identical earliest year of study, we considered them equal in chronological order.

We plotted the effect sizes across generations against placebo or no treatment and against the predecessor and converted the effect sizes to natural logarithm to standardise the *Y*-axis scale. We presented our results descriptively and analysed the trend in the effect sizes across generations using Mann-Kendall test, with a p of <0.05 indicating statistical significance (Kendall package, R Studio 4.1.2, 2022).

Results

From 8,048 records retrieved, we identified 30 neonatal NMAs, shortlisted 18 NMAs on pharmacological interventions, and included 10 NMAs. Eight shortlisted NMAs were excluded for the following reasons: interventions evaluated were mainly non-pharmacological ($n = 1$), evaluation of one single drug in different doses ($n = 1$) and overlapping evidence with larger included NMAs ($n = 6$).

The 10 NMAs included 352 RCTs and 102,653 participants, with 61 different interventions. Table 1 displays the characteristics of each included NMA. The topics evaluated included the effectiveness of prophylactic cyclo-oxygenase inhibitors to prevent mortality and morbidities, antiepileptic medications for neonatal seizures, types of corticosteroid in preventing BPD, corticosteroid administration regimen for preventing BPD, food additives for preventing NEC, immunotherapy for treatment of sepsis, interventions for infantile haemangioma, interventions for PDA, probiotics for preventing NEC, and surfactant for respiratory distress syndrome.

Table 1. Characteristics of included neonatal NMAs that evaluated pharmacological interventions

Reference	Year	Topic evaluated	Interventions evaluated	Outcomes	Studies, *n*	Cumulative participant	Earliest study, year	Latest study, year
Chi et al. [11]	2021	Probiotics for preventing NEC	Bacillus, Bifidobacterium, BL, BLE, BLP, BLSA, BLST, BP, BST, Lactobacillus, LP, Nystatin, Saccharomyces	NEC, NEC-mortality[a]	45	12,320	2002	2018
Li et al. [12]	2019	Immunotherapy for treatment of sepsis	IgG, IgGAM, GCSF, GMCSF	All-cause mortality[a], duration of hospital stay	27	4,872	1981	2015
Mitra et al. [13]	2022	Prophylactic cyclo-oxygenase inhibitors to prevent mortality and morbidities	Indomethacin, ibuprofen, paracetamol	Mortality[a], severe IVH, NEC, surgical PDA closure, GI perforation, chronic lung disease, cerebral palsy	28	3,999	1985	2018
Mitra et al. [14]	2018	Interventions for PDA	Ibuprofen, high oral dose, ibuprofen, standard oral dose, ibuprofen, high IV dose, ibuprofen, standard IV dose bolus, ibuprofen, continuous IV infusion, acetaminophen, oral, indomethacin, IV bolus, indomethacin, continuous IV infusion, indomethacin, other types of administration	PDA closure[a]	68	4,802	1981	2017
Ramaswamy et al. [15]	2021	Corticosteroid administration regimen for preventing BPD	EHC, EIBEC, EIBUD, EIFLUT, ITBUD, LaHdDx, LaLdDx, LaMdDx, LHC, LIBEC, LIBUD, MoHdDx, MoLdDx, MoMdDx	BPD or mortality[a]	62	5,559	1989	2018
Xu et al. [16]	2021	Antiepileptic medications for neonatal seizures	Phenobarbital, phenytoin, levetiracetam, lorazepam, lidocaine, midazolam, clonazepam	Cessation of neonatal seizure[a]	11	1,333	1999	2020

Table 1 (continued)

Reference	Year	Topic evaluated	Interventions evaluated	Outcomes	Studies, *n*	Cumulative participant	Earliest study, year	Latest study, year
Yang [17]	2020	Interventions for reducing infantile haemangioma	Oral propranolol, intralesional glucocorticoid, topical propranolol/ timolol, oral glucocorticoid, intralesional propranolol, oral captopril, laser (included as this was the only non-pharmacological intervention evaluated)	Haemangioma reduction or resolution[a]	20	1,149	2002	2017
Yu et al. [18]	2017	Additives for preventing NEC	Probiotic, pentoxifylline, lactoferrin, probiotic + fructo-oligosaccharides, arginine	NEC[a]	27	4,649	1999	2016
Zeng et al. [19]	2018	Types of corticosteroid in preventing BPD	Dexamethasone high dose, dexamethasone low dose, hydrocortisone, budesonide, beclomethasone, fluticasone	BPD[a]	47	6,747	1972	2016
Zhang et al. [20]	2015	Surfactant types for respiratory distress syndrome	Curosurf, Survanta, Infasurf, Exosurf, Surfaxin, Alveofact	Neonatal mortality[a]	17	57,223	1995	2013

[a]Selected outcomes.

Against Placebo/No Treatment

Across 8 NMAs, there were 61 comparisons with placebo or no treatment. Point estimates favoured the intervention in 91.8% (56/61) of comparisons, with 37.7% (23/61) of cases reaching statistical significance. However, no significant trend was observed in effect sizes across generations (tau −0.06 to 0.467, $p = 0.2–1$).

Against the Previous Generation

Across 10 NMAs, there were 72 comparisons between a newer intervention and its predecessor (Fig. 1). In 47 comparisons (65.3%), point estimate favoured the newer intervention, though this reached statistical significance in only the following 3 comparisons (4.2%): (i) oral high dose versus intravenous continuous infusion of ibuprofen for failure of PDA closure (OR: 0.2, 95% CI: 0.06–0.64); (ii) moderately early-initiated, medium cumulative dose (MoMdDx) versus late-initiated, medium cumulative dose of dexamethasone (LaMdDx) regimen for reduction of BPD or mortality (RR: 0.64, 95% CI: 0.45–0.94); and (iii) dexamethasone (high dose) versus hydrocortisone for reduction of BPD (OR: 0.4, 95% CI: 0.18–0.83). In contrast, the newer interventions were significantly less efficacious than older intervention in the following 2 comparisons: (i) intravenous continuous infusion of ibuprofen versus oral paracetamol for failure of PDA closure (OR: 4.08, 95% CI: 1.35–12.5) and (ii) phenytoin versus phenobarbitone for neonatal seizure (OR: 1.33, 95% CI: 1.20–9.09) (please see online suppl. Table; for all online suppl. material, see https://doi.org/10.1159/000539729, for a detailed tabulation of the comparisons).

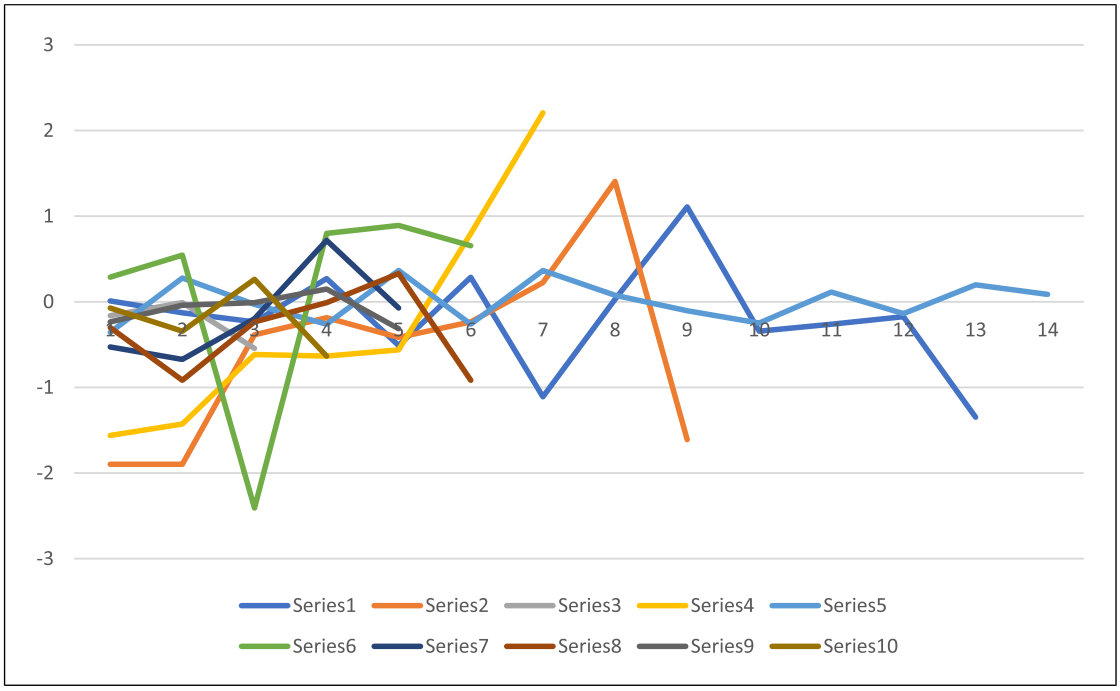

Fig. 1. The effect size of a medication compared against the medication of a previous generation (x axis represents the sequence of generation; y axis represents the effect sizes in natural logarithmic scale). Series 1: probiotics for the prevention of NEC in preterm infants. Series 2: medications for the reduction of haemodynamically significant PDA in preterm infants. Series 3: prophylactic cyclo-oxygenase inhibitor drugs for the prevention of mortality in preterm infants. Series 4: pharmacological treatments for reduction of infantile haemangiomas. Series 5: postnatal corticosteroids regimen for the prevention of bronchopulmonary dysplasia in preterm neonates. Series 6: antiepileptic drugs for the prevention of neonatal seizures*. Series 7: food additives for the prevention of NEC in neonates. Series 8: different types of corticosteroids for the prevention of BPD in preterm infants. Series 9: exogenous pulmonary surfactants on mortality rate in neonatal RDS*. Series 10: immunotherapy on mortality in neonates with suspected or proven sepsis. *No data on comparison with placebo/no treatment.

In most comparisons, differences between generations were small and inconsistent, with no significant trend observed (tau −0.3 to +0.6, p = 0.09–1). In one NMA that evaluated treatments for haemangioma reduction [17], the point estimates appeared to show a worsening trend on the effects of newer interventions (tau: 0.905, p = 0.007). However, most of the effects were accompanied by wide 95% confidence intervals, and none were statistically significant.

Discussion

Our study found no evidence that newer neonatal pharmacological interventions are progressively more efficacious than the older interventions. Certain interventions were found to be significantly more efficacious than their predecessors, for example, oral ibuprofen in high dosage compared to intravenous ibuprofen for PDA closure, earlier initiation of medium-dose dexamethasone compared to later initiation for BPD or mortality and high-dose dexamethasone compared to hydrocortisone for BPD. Nonetheless, overall, the differences between generations appear small and inconsistent. There is an intriguing pattern of apparently decreasing efficacy with newer medications for reducing infantile haemangioma judging by the point estimate. However, all differences were not statistically significant, and most comparisons were very imprecise as indicated by wide 95% confidence intervals, hence precluding a clear conclusion.

Our findings echo previous reports in adult medicine. Djulbegovic et al. [21] examined 860 RCTs and found that only around half of the studies demonstrated superiority of a new treatment against the current best treatment, without a clear time trend. The finding supports the need for individualised decision-making, as the effect, perceived benefit-harm balance, and acceptability of an intervention may vary according to individuals [22]. However, effective communication of evidence remains a major challenge for physicians. Clinical practice guidelines help provide overall recommendations but may not provide sufficient details on the benefits and risks of all options to facilitate informed

decisions [23]. Use of specialised tools like visual aids based on robust synthesised evidence like what we have attempted to undertake here may help communicate evidence [24].

We acknowledge the following limitations. First, we included only NMAs of RCTs, which captured only a small proportion of the relevant evidence. We acknowledge that some good sources of evidence from RCTs that were not included in NMAs or from well-conducted non-randomised studies were not incorporated. The range of conditions and interventions covered in our included NMAs, some of which are out of date, are not representative of the full range of major neonatal conditions. We could not perform novel NMAs or incorporate data from pairwise meta-analyses due to resource constraints. Next, as most currently published NMAs are non-Cochrane, there might be issues on the rigour of the review process, as Cochrane reviews have been shown to be more robust and comprehensive than non-Cochrane reviews [25]. We used the earliest trial as a proxy for drug availability, which might not reflect real-world uptake of the medication. We focused on one patient-important outcome per NMA, while many NMAs included multiple outcomes. Finally, we only included outcomes on efficacy and not safety, which should be considered in determining the overall superiority of the intervention and its desirability for patients and care providers.

Conclusions

This study provides evidence against routine preference of newest medications and supports individualised decision-making in neonatal care. Continued synthesis of comparative effectiveness evidence through high-quality NMAs can help facilitate efforts to this end.

Acknowledgment

We would like to thank Dr. Pantakarn Saidung for his contribution in screening and selection in the initial stage of the study.

Statement of Ethics

This study examined only published research data and so did not undergo the ethics approval process. The study protocol was registered at PROSPERO (CRD42022333299).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was not supported by any sponsor or funder.

Author Contributions

Lai N.M. conceived the study, wrote the protocol, selected the studies, extracted and analysed the data, and wrote the manuscript. Veettil S.K. selected the studies, analysed and interpreted the data, and wrote the manuscript. Chaiyakunapruk N. wrote the protocol, interpreted the data, and provided critical intellectual input to the manuscript. Glasziou P. interpreted the data and provided critical intellectual input to the manuscript.

Data Availability Statement

All data of the study, including datasets and analysis results, will be made available upon reasonable request to the corresponding author.

References

1 Allegaert K, van den Anker J. Neonatal drug therapy: the first frontier of therapeutics for children. Clin Pharmacol Ther. 2015;98(3):288–97. https://doi.org/10.1002/cpt.166

2 Zeitlin J, Manktelow BN, Piedvache A, Cuttini M, Boyle E, van Heijst A, et al. Use of evidence based practices to improve survival without severe morbidity for very preterm infants: results from the EPICE population based cohort. BMJ. 2016;354:i2976. https://doi.org/10.1136/bmj.i2976

3 Mandel D, Littner Y, Mimouni FB, Lubetzky R. Conclusiveness of the cochrane neonatal reviews: a systematic analysis. Acta Paediatr. 2006;95(10):1209–12. https://doi.org/10.1080/08035250600580537

4 Lai NM, Ong JM, Chen KH, Chaiyakunapruk N, Ovelman C, Soll R. Decreasing number of conclusive neonatal reviews: increasing role for shared decision-making? Neonatology. 2020;117(1):125–6. https://doi.org/10.1159/000502492

5 Lipstein EA, Brinkman WB, Fiks AG, Hendrix KS, Kryworuchko J, Miller VA, et al. An emerging field of research: challenges in pediatric decision making. Med Decis Making. 2015;35(3):403–8. https://doi.org/10.1177/0272989X14546901

6 Fein MN, Fischer DA, O'Keefe AW, Sussman GL. CSACI position statement: newer generation H(1)-antihistamines are safer than first-generation H(1)-antihistamines and should be the first-line antihistamines for the treatment of allergic rhinitis and urticaria. Allergy Asthma Clin Immunol. 2019;15:61. https://doi.org/10.1186/s13223-019-0375-9

7 French JA, Gazzola DM. New generation antiepileptic drugs: what do they offer in terms of improved tolerability and safety? Ther Adv Drug Saf. 2011;2(4):141–58. https://doi.org/10.1177/2042098611411127

8 Carvalho AF, Sharma MS, Brunoni AR, Vieta E, Fava GA. The safety, tolerability and risks associated with the use of newer generation antidepressant drugs: a critical review of the literature. Psychother Psychosom. 2016;85(5):270–88. https://doi.org/10.1159/000447034
9 Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ. 2005;331(7521):897–900. https://doi.org/10.1136/bmj.331.7521.897
10 Webbe JWH, Duffy JMN, Afonso E, Al-Muzaffar I, Brunton G, Greenough A, et al. Core outcomes in neonatology: development of a core outcome set for neonatal research. Arch Dis Child Fetal Neonatal Ed. 2020;105(4):425–31. https://doi.org/10.1136/archdischild-2019-317501
11 Chi C, Li C, Buys N, Wang W, Yin C, Sun J. Effects of probiotics in preterm infants: a network meta-analysis. Pediatrics. 2021;147(1):e20200706. https://doi.org/10.1542/peds.2020-0706
12 Li Y, Yang S, Wang G, Liu M, Zhang Z, Liu H, et al. Effects of immunotherapy on mortality in neonates with suspected or proven sepsis: a systematic review and network meta-analysis. BMC Pediatr. 2019;19(1):270. https://doi.org/10.1186/s12887-019-1609-1
13 Mitra S, Florez ID, Tamayo ME, Mbuagbaw L, Vanniyasingam T, Veroniki AA, et al. Association of placebo, indomethacin, ibuprofen, and acetaminophen with closure of hemodynamically significant patent ductus arteriosus in preterm infants: a systematic review and meta-analysis. JAMA. 2018;319(12):1221–38. https://doi.org/10.1001/jama.2018.1896
14 Mitra S, Gardner CE, MacLellan A, Disher T, Styranko DM, Campbell-Yeo M, et al. Prophylactic cyclo-oxygenase inhibitor drugs for the prevention of morbidity and mortality in preterm infants: a network meta-analysis. Cochrane Database Syst Rev. 2022;4(4). https://doi.org/10.1002/14651858.CD013846.pub2
15 Ramaswamy VV, Bandyopadhyay T, Nanda D, Bandiya P, Ahmed J, Garg A, et al. Assessment of postnatal corticosteroids for the prevention of bronchopulmonary dysplasia in preterm neonates: a systematic review and network meta-analysis. JAMA Pediatr. 2021;175(6):e206826. https://doi.org/10.1001/jamapediatrics.2020.6826
16 Xu ZE, Li WB, Qiao MY, Cui HT, Zhao LZ, Chen QX, et al. Comparative efficacy of antiepileptic drugs for neonatal seizures: a network meta-analysis. Pediatr Neonatol. 2021;62(6):598–605. https://doi.org/10.1016/j.pedneo.2021.06.005
17 Yang H, Hu DL, Xuan XX, Chen JJ, Xu S, Wu XJ, et al. The efficacy and safety of treatments for infantile hemangiomas: a Bayesian network meta-analysis. Int J Dermatol. 2020;59(11):1320–31. https://doi.org/10.1111/ijd.15015
18 Yu W, Sui W, Mu L, Yi W, Li H, Wei L, et al. Preventing necrotizing enterocolitis by food additives in neonates: a network meta-analysis revealing the efficacy and safety. Medicine. 2017;96(21):e6652. https://doi.org/10.1097/MD.0000000000006652
19 Zeng L, Tian J, Song F, Li W, Jiang L, Gui G, et al. Corticosteroids for the prevention of bronchopulmonary dysplasia in preterm infants: a network meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2018;103(6):F506–11. https://doi.org/10.1136/archdischild-2017-313759
20 Zhang L, Cao HY, Zhao S, Yuan LJ, Han D, Jiang H, et al. Effect of exogenous pulmonary surfactants on mortality rate in neonatal respiratory distress syndrome: a network meta-analysis of randomized controlled trials. Pulm Pharmacol Ther. 2015;34:46–54. https://doi.org/10.1016/j.pupt.2015.08.005
21 Djulbegovic B, Kumar A, Glasziou PP, Perera R, Reljic T, Dent L, et al. New treatments compared to established treatments in randomized trials. Cochrane Database Syst Rev. 2012;10:Mr000024. https://doi.org/10.1002/14651858.MR000024.pub3
22 US Preventive Services Task Force; Davidson KW, Mangione CM, Barry MJ, Nicholson WK, Cabana MD, et al. Collaboration and shared decision-making between patients and clinicians in preventive health care decisions and US preventive services task force recommendations. JAMA. 2022;327(12):1171–6. https://doi.org/10.1001/jama.2022.3267
23 Woolf SH, Grol R, Hutchinson A, Eccles M, Grimshaw J. Clinical guidelines: potential benefits, limitations, and harms of clinical guidelines. BMJ. 1999;318(7182):527–30. https://doi.org/10.1136/bmj.318.7182.527
24 Mercer MB, Rose SL, Talerico C, Wells BJ, Manne M, Vakharia N, et al. Use of visual decision aids in physician-patient communication: a pilot investigation. J Patient Exp. 2018;5(3):167–76. https://doi.org/10.1177/2374373517746177
25 Jadad AR, Cook DJ, Jones A, Klassen TP, Tugwell P, Moher M, et al. Methodology and reports of systematic reviews and meta-analyses: a comparison of cochrane reviews with articles published in paper-based journals. JAMA. 1998;280(3):278–80. https://doi.org/10.1001/jama.280.3.278