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Use and safety of azithromycin in neonates: a systematic review

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USE AND SAFETY OF AZITHROMYCIN IN NEONATES: A SYSTEMATIC REVIEW

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Keywords – Azithromycin, safety, neonates, adverse events

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ABSTRACT

Objectives: To identify the use and adverse drug reactions associated with azithromycin in neonates.

Setting: Databases MEDLINE (1948 – November 2014), EMBASE (1980 – November 2014), and Pubmed (November 2014) were searched for studies on azithromycin in neonates.

Participants: All studies involving neonates (<28 days old) who have received at least a single dose of azithromycin for which safety was evaluated.

Primary and secondary outcome measures: The primary outcome was adverse event (AE) of azithromycin. Use of azithromycin in neonates was the secondary outcome.

Results: A total of 10 articles involving 315 neonates were identified. Three hundred and seventy one AEs were reported. Adverse events were mainly respiratory (358/1000 neonate), neurological (273/1000 neonates), and gastrointestinal (196/1000 neonates) in origin. Azithromycin significantly reduced the risk of bronchopulmonary dysplasia in extremely premature neonates [RR=0.83, 95% CI: 0.71-0.98, p=0.02]. There was no significant difference in the incidence of elevated liver enzymes between azithromycin and placebo group (p=0.76). Compared with erythromycin, azithromycin treated neonates developed fewer adverse reactions.

Conclusions: Azithromycin significantly reduces the risk of BPD in preterm neonates. It has a better safety profile than erythromycin in the limited number of treated neonates.

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. This systematic review assessed the quality of all the RCTs
2. Randomised controlled trials (RCTs), cohort studies and case reports were reviewed.
3. Only a few studies of azithromycin in neonates have been published.

INTRODUCTION

Azithromycin is a macrolide derivative of erythromycin. It is one of the most commonly prescribed antibiotics in children, with a prescription rate of between 4-14%.[1-3] Since its approval in the USA and Europe,[4,5] it has been used extensively for the treatment of several paediatric infectious diseases. [6] Prescription rate for respiratory tract infection in children is increasing.[3]

Due to lack of efficacy and safety studies, oral and intravenous formulations are not recommended for children less than 6 months[7] and 16 years,[8] respectively. The safety of azithromycin eye drops in children under one year is also unknown.[9,10] Gastrointestinal disorders such as diarrhoea, vomiting and abdominal pain are the most commonly reported side effects in paediatrics.[11] Increased risk of arrhythmia and cardiovascular related death in adults has been reported.[12, 13]

The potential of azithromycin as a chemoprophylactic agent for Bronchopulmonary Dysplasia (BPD) in neonates is still under exploration. *Ureaplasma Urealyticum,* which has been shown to be susceptible to the drug,[14,15] is associated with BPD.[16,17] Despite limited efficacy and safety data, the US Centre for Disease Control (CDC) considers azithromycin as the first choice treatment and chemoprophylaxis of choice for pertussis in neonates.[18]

There is currently insufficient information on azithromycin treatment in neonates; therefore, this systematic review aims to evaluate all published data and reports on the safety and use of the drug in this age group.

METHODS

This review was done as per PRISMA guideline (Appendix 1). The systematic review protocol was not published.

Search strategy

The databases MEDLINE (1948 – November 2014), EMBASE (1980 – November 2014), and Pubmed (November 2014) were searched. MeSH words such as 'preterm or neonat* or neonate* or newborn* or infan*' were combined with 'azithromycin' in title. Manual search of bibliography was also done.

Eligibility criteria

Any published literature with documented involvement of neonates (birth-28 days) administered azithromycin via any route of administration for any disease condition. There was no restriction on the type of study that was included, publication date and language of publication or inclusion of abstracts. Any article with involvement of the specified age group taking at least a single dose of azithromycin was assessed. Only articles with information on the safety of azithromycin were included, such as any mention of an adverse drug reaction, drug toxicity, drug, side effects or adverse event.

Data quality assessment

The Randomized controlled trials (RCTs) were assessed using the Cochrane collaboration's tool for assessing risk of bias [19] by two independent reviewers (Appendix 3). Studies with low risk of bias in at least four of the six parameters were included in the meta-analysis.

Data collection and statistical analysis

A single reviewer undertook eligibility assessment. Each title and available abstract was screened for appropriateness and relevant articles obtained. Articles were examined independently by a second reviewer to confirm they met inclusion criteria. Hand searching of references of articles was done. Data was extracted from relevant articles on methodology, characteristics of trial participants (including condition and gestational age),

number of neonates receiving azithromycin, number of participants in study, route of administration, dose, duration of azithromycin treatment, comparator drugs and adverse events.

Meta-analyses was carried out in Revman version 5.3. Relative risks and 95% confidence intervals were estimated for each RCT. Overall relative risks were calculated from the RCTs. Begg and Mazumdar's rank correlation tests were used to assess publication bias. No significant publication bias was found. Between studies heterogeneity was assessed using a Chi-squared test where a p-value less than 0.05 indicated significant heterogeneity. Fixed effect models were used to produce summary relative risks and 95% confidence intervals where heterogeneity did not exist. If statistical heterogeneity did exist then random effects models were applied.

RESULTS

A total of 10 articles involving 315 neonates were identified (Figure 1). The majority of the studies (4 studies) were RCTs. There were 3 pharmacokinetic studies and 2 cohort studies (Table 1). One case report was identified. The RCTs involved 211 neonates who received azithromycin and 198 controls. The cohort studies and PK studies involved 70 and 43 neonates respectively. Three hundred and seventy one AEs were reported. Adverse events were mainly respiratory (358/1000 neonate), neurological (273/1000 neonates), and gastrointestinal (196/1000 neonates) in origin. Vomiting (44/1000 neonates), diarrhoea (15/1000 neonates) abdominal tenderness (22/1000 neonates) and feeding intolerance (37/1000 neonates) were the most frequently reported gastrointestinal symptoms. The majority of the respiratory and neurological AEs were prematurity related (Table 2).

Evidence from RCTs

Two of the 4 RCTs were placebo controlled. 10mg/kg/d of intravenous azithromycin was administered for one week followed by a 5 week course of 5mg/kg/d as prophylaxis for BPD

in both studies. [20,21] A third study administered 5mg/kg/d for 1 week after an initial 1 week course of oral 10mg/kg/d. [22] The patients in the comparator arm of this study were not given any treatment. Meta-analysis of the incidence of BPD between neonates administered azithromycin and the control group in the three studies showed that azithromycin significantly reduced the risk of BPD in extremely premature neonates [RR=0.83, 95% CI: 0.71-0.98, p=0.02] (Figure 2). While 55% of preterm neonates given azithromycin developed BPD compared to 67% of those without treatment or given placebo.

The fourth study compared the efficacy of azithromycin with erythromycin for the treatment of chlamydia conjunctivitis. [23] Ninety-six percent of children treated with 3 days intravenous 10mg/kg and subsequent 4 days oral dose azithromycin recovered compared with 76% of those given twice daily 10mg/kg erythromycin for 3 days followed by 11 days of thrice daily oral erythromycin. A significantly higher cure rate (p=0.03) was achieved with azithromycin than erythromycin.

There was no significant difference in the incidence of elevated liver enzymes between azithromycin and placebo group (p=0.76) (Figure 3). All cases of elevated transaminases (16 cases) were reported in a single RCT.[20] There were 13 cases of elevated transaminases in the control group of this study. Only one placebo/no treatment controlled trial reported vomiting as an adverse event, with no significant difference between the azithromycin group and the neonates without treatment (p=0.79) (Figure 3). The other AEs reported in the placebo/no treatment controlled RCTs were prematurity related (intraventricular haemorrhage, periventricular leucomalacia, necrotizing enterocolitis, patent ductus arteriosus and hearing abnormalities) and there were no significant differences between azithromycin and the comparator arms. [20-22]

For the erythromycin controlled trial for chlamydia conjunctivitis, there were significantly less cases of abdominal pain (p=0.0009), diarrhoea (p= 0.005) and decreased appetite (p= <0.0001) seen in the azithromycin group. The incidence of vomiting was not significantly different (p=1.000).[23]

Evidence from observational studies

Two cohort studies were identified. One of these studies involved a cohort of neonates given either azithromycin or erythromycin following exposure to a patient with pertussis.[24] Fifty eight neonates received azithromycin while 18 were given erythromycin. None of the neonates developed pertussis. Fourteen (24%) of those given azithromycin experienced AEs. These included 3 cases each of irritability, candidiasis and vomiting; 2 cases of rash and one case each of diarrhoea, abdominal pain and blood in the stool. Ten (56%) of the neonates given erythromycin experienced AEs. There was a significantly lower incidence of diarrhoea (p=0.01) in the azithromycin treated compared with erythromycin treated neonates. The incidences of other AEs were not significantly different.

The second observational study involved twelve neonates who received varying doses of azithromycin suspension for the treatment of chlamydia conjunctivitis.[25] Three of the 5 neonates (60%) administered a single dose of 20mg/kg became culture negative; while 6 of the 7 (86%) given 20mg/kg/d for three days became culture negative. No AEs were reported in this study

Pharmacokinetic studies

A single dose 20mg/kg was administered in a pharmacokinetic study[26] and 10mg/kg single dose administered in two other pharmacokinetic studies.[27,28] All the AEs reported in two of these studies were prematurity related and none was attributed to azithromycin. [26, 27] There were 4 cases of intraventricular haemorrhage, 3 of hearing loss, 2 of necrotising enterocolitis, 1 each of periventricular leucomalacia, respiratory distress syndrome, pneumomediastinum and hyperbilirubinemia. No AEs were observed in the third study.[28]

Case report

There was one case report of pyloric stenosis in a 5 week old infant who had received 5 days of oral azithromycin at 3 weeks of life as treatment for chlamydia conjunctivitis. [29]

DISCUSSION

Only a small population of neonates have been treated with azithromycin and no major AE has been documented. This systematic review shows that azithromycin significantly reduces the risk of BPD in neonates and is also effective in the treatment of chlamydia conjunctivitis. A previous study has demonstrated the efficacy of a similarly structured antibiotic, clarithromycin, in the prevention of BPD.[30] Macrolide antibiotics are inhibitors of *Ureaplasma Urealyticum,* which are involved in the pathogenesis of BPD.[15, 17] We have also identified two off- label studies demonstrating the efficacy of azithromycin against chlamydia trachomatis in neonates. Previous studies have reported the susceptibility of chlamydia to azithromycin.[31]

The majority of the AEs reported in preterm neonates were related to prematurity and were unlikely to be caused by azithromycin. Results from one of the studies showed that azithromycin had a better safety profile than erythromycin in neonates. Diarrhoea, abdominal discomfort and reduced appetite were significantly less in azithromycin treated neonates. There had been several reports of pyloric stenosis resulting from erythromycin use in neonates,[32,33] however, only one case report of azithromycin related neonatal pyloric stenosis was identified in this review. This may be due to the limited usage of the drug in this age group. There had been two previous case reports of pyloric stenosis associated with azithromycin in infants.[34]

Although arrhythmias had been reported in azithromycin treated adults; [35, 36] none of the reviewed studies evaluated neonates for arrhythmia. There is a documented case of arrhythmia in an infant following azithromycin overdose[37] and spiramycin, which is a structurally similar macrolide has been associated with neonatal arrhythmia. [38]

In conclusion, azithromycin significantly reduces the risk of BPD in preterm neonates and it is effective for the treatment of chlamydia conjunctivitis. It has a better safety profile than erythromycin in the limited number of treated neonates.

Table 1: Summary of all included studies

Reference	Study type	Comparator	No of patients AZT	No of patients control	Number of AEs	AZT dose	Indication	Country
Ballard et al (2011)[20]	RCT	Placebo	111	109	231	10mg/kg x 1wk then 5mg/kg/d x 5wks (IV)	BPD	USA
Ballard et al (2007)[21]	RCT	Placebo	19	16	39	10mg/kg x 1wk then 5mg/kg/d x 5wks (IV)	BPD	USA
Gharehbaghi et al (2011)[22]	RCT	Nil	56	52	52	10mg/kg x 1wk then 5mg/kg/d x 1wk (oral)	BPD	Iran
Dong (2005)[23]	RCT	Erythromycin	25	21	18	10mg/kg x3 days(IV) then 10mg/kg x3 days (oral)	Chlamydia	China
Friedman et al (2004)[24]	Cohort	-	58	-	13	10-12mg/kg x 5 days (oral)	Pertussis	USA
Hammerschlag et al (1998)[25]	Cohort	-	12	-	0	20mg/kg single dose and 20mg/kg/d x 3 days (oral)	Chlamydia	USA
Viscardi et al (2013)[26]	Pharmacokinetic	-	13	-	7	20mg/kg stat	U. Urealyticum	USA
Hassan et al (2010)[27]	Pharmacokinetic	-	14	-	10	10mg/kg stat	BPD	USA
Tessema et al (2007)[28]	Pharmacokinetic	-	16	-	0	10mg/kg stat	-	USA
Zayas et al (2010)[29]	Case report	-	1	-	1	NA	Chlamydia	USA

Table 2: Classification and risk of adverse events from RCTs and observational studies (n=371)

Classification	Adverse Event	Number	Risk of AE per 1000 neonates
Gastrointestinal	Vomiting	12	44
	Feeding intolerance/poor feeding	10	37
	NEC	8	30
	Abdominal tenderness	6	22
	Diarrhoea	4	15
	Other gastrointestinal symptoms	13	48
		53	**196**
Respiratory	BPD	96	354
	Respiratory distress	1	4
		97	**358**
CNS	At least grade 3 IVH	29	107
	Abnormal hearing	22	81
	PVL	15	55
	Others	4	15
		74	**273**
Hepatobiliary	Elevated transaminase	**16**	**59**
Cardiovascular	PDA	**20**	**74**
Metabolic	Hyperkalaemia	**2**	**7**
Others	Sepsis	11	41
	Other infections	96	354
	Allergy	2	7
Total		**371**	

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CONTIBUTORSHIP

IC, SK, EJ, and HS conceived the idea; CS performed the literature search and extracted the data. OE updated the search and verified the extracted data. OE produced the first draft of the manuscript. All authors contributed to the subsequent and final drafts of the manuscript.

FUNDING

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Competing interest: None

Image legend

Figure 1: Flow chart of included articles

Figure 2: Relative risks of BPD in azithromycin and untreated/placebo treated preterm neonates.

Figure 3: Relative risk of elevated transaminase in Azithromycin and placebo treated neonates.

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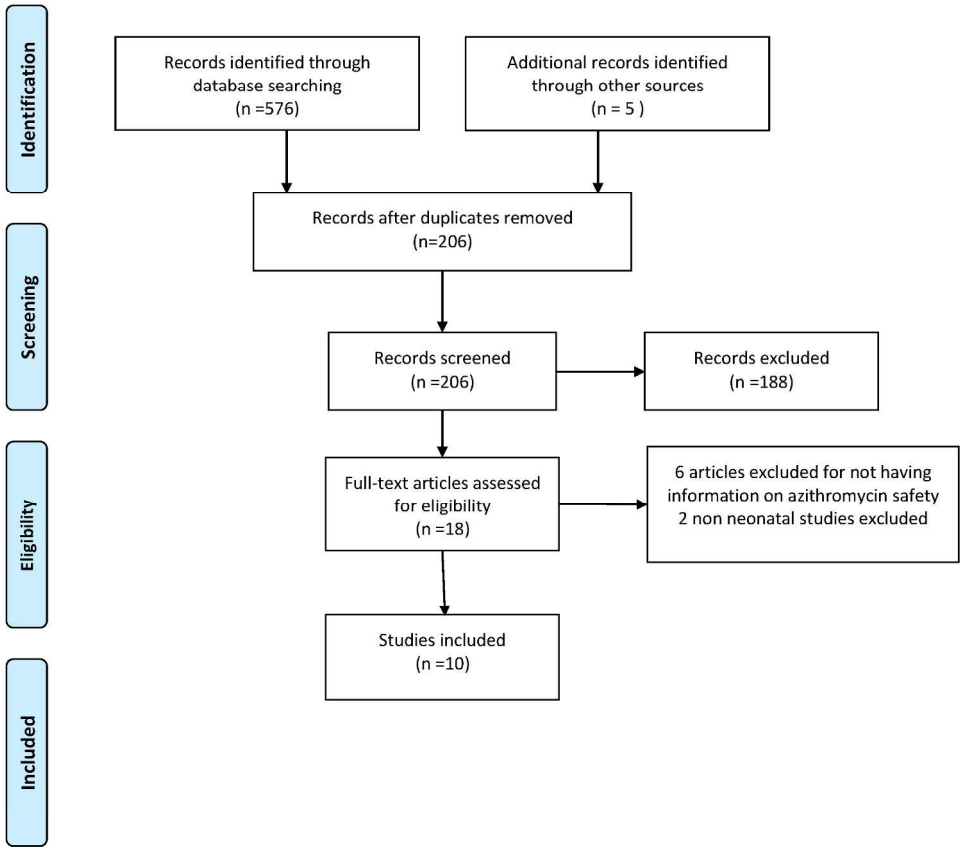

Flow chart of included articles
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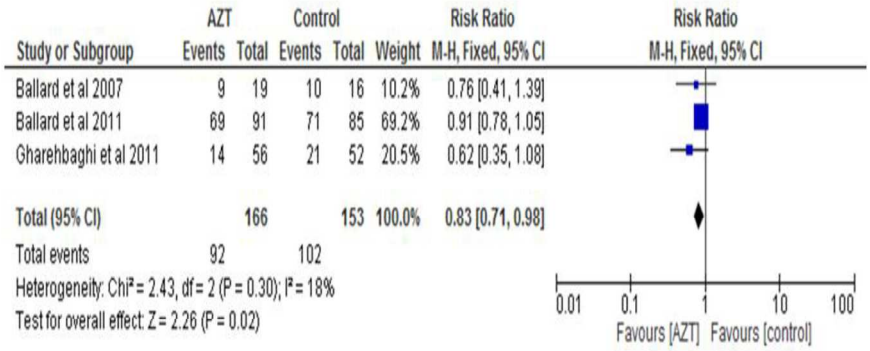

Relative risks of BPD in azithromycin and untreated/placebo treated preterm neonates.
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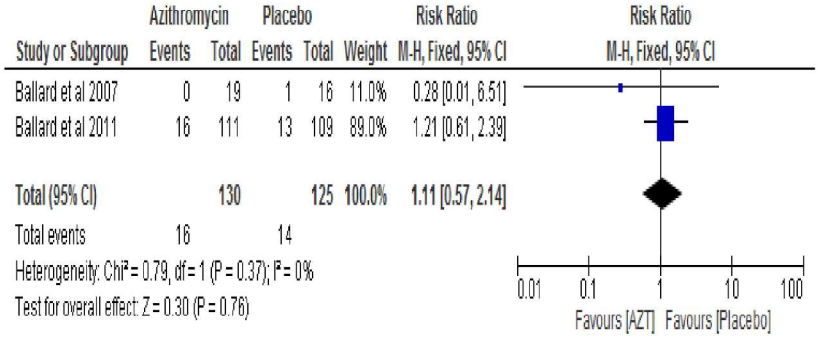

Relative risk of elevated transaminase in azithromycin and placebo treated neonates.
297x210mm (300 x 300 DPI)

PRISMA Checklist: USE AND SAFETY OF AZITHROMYCIN IN NEONATES: SYSTEMATIC REVIEW

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	p1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	p2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	P4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	p4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	P5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	P5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	P5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	p5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	p5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	p5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	P6

PRISMA Checklist: USE AND SAFETY OF AZITHROMYCIN IN NEONATES: SYSTEMATIC REVIEW

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	P6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not applicable
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 2&3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	p7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Appendix 1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	P9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	P9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P9

PRISMA Checklist: USE AND SAFETY OF AZITHROMYCIN IN NEONATES: SYSTEMATIC REVIEW

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	P13

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COCHRANE RISK OF BIAS ASSESSMENT

	Gharehbaghi et al (2012)	Ballard et al. (2011)	Ballard et al (2007)	*Dong et al (2007)
Random sequence generation	Low	Low	Low	Unclear
Allocation cocealment	Low	Low	Low	Unclear
Blinding of participants	High	Unclear	Low	Unclear
Incomplete data outcome	Low	Low	Low	Unclear
Selective reporting	Low	Low	Low	Unclear
Blinding outcome	High	Low	Low	Unclear

*Article in Chinese

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Use and safety of azithromycin in neonates: a systematic review

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Keywords:	CLINICAL PHARMACOLOGY, NEONATOLOGY, Adverse events < THERAPEUTICS

USE AND SAFETY OF AZITHROMYCIN IN NEONATES: A SYSTEMATIC REVIEW

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ABSTRACT

Objectives: To identify the use and adverse drug reactions associated with azithromycin in neonates.

Setting: Databases MEDLINE (1948–August 2015), EMBASE (1980 – August 2015), and Pubmed (August 2015) were searched for studies on azithromycin in neonates.

Participants: All studies involving neonates (<28 days old) who have received at least a single dose of azithromycin for which safety was evaluated.

Primary and secondary outcome measures: The primary outcome was adverse event (AE) of azithromycin. Use of azithromycin in neonates was the secondary outcome.

Results: A total of 11 articles involving 473 neonates were identified. Three hundred and seventy one AEs were reported. Adverse events were mainly respiratory (358/1000 neonate), neurological (273/1000 neonates), and gastrointestinal (196/1000 neonates) in origin. Azithromycin significantly reduced the risk of bronchopulmonary dysplasia in extremely premature neonates [RR=0.83, 95% CI: 0.71-0.98, p=0.02]. There was no significant difference in the incidence of elevated liver enzymes between azithromycin and placebo group (p=0.76). There were 4 cases of infantile hypertrophic pyloric stenosis (IHPS).

Conclusions: Azithromycin significantly reduces the risk of BPD in preterm neonates. The relationship between azithromycin and IHPS requires further investigation.

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. This systematic review assessed the quality of all the RCTs
2. Randomised controlled trials (RCTs), cohort studies and case reports were reviewed.
3. Only a few studies of azithromycin in neonates have been published.

INTRODUCTION

Azithromycin is a macrolide derivative of erythromycin. It is one of the most commonly prescribed antibiotics in children, with a prescription rate of between 4-14%.[1-3] Since its approval in the USA and Europe,[4,5] it has been used extensively for the treatment of several paediatric infectious diseases. [6] Prescription rate for respiratory tract infection in children is increasing.[3]

Due to lack of efficacy and safety studies, oral and intravenous formulations are not recommended for children less than 6 months[7] and 16 years,[8] respectively. The safety of azithromycin eye drops in children under one year is also unknown.[9,10] Gastrointestinal disorders such as diarrhoea, vomiting and abdominal pain are the most commonly reported side effects in paediatrics.[11] Increased risk of arrhythmia and cardiovascular related death in adults has been reported.[12, 13]

The potential of azithromycin as a chemoprophylactic agent for Bronchopulmonary Dysplasia (BPD) in neonates is still under exploration. Ureaplasma infection, which has been shown to be susceptible to the drug,[14,15] is associated with BPD.[16,17] Despite limited efficacy and safety data, the US Centre for Disease Control (CDC) considers azithromycin as the first choice treatment and chemoprophylaxis of choice for pertussis in neonates.[18]

There is currently insufficient information on azithromycin treatment in neonates; therefore, this systematic review aims to evaluate all published data and reports on the safety and use of the drug in this age group.

METHODS

This review was done as per PRISMA guideline. The systematic review protocol was not published.

Search strategy

The databases MEDLINE (1948 – August 2015), EMBASE (1980 – August 2015), and Pubmed (up to August 2015) were searched. Search words: 'preterm or neonat* or neonate* or newborn* or infan*' in title and abstract were combined with 'azithromycin' in title and abstract for all databases. Manual search of bibliography was also done.

Eligibility criteria

Any published literature with documented involvement of neonates (birth-28 days) administered azithromycin via any route of administration for any disease condition. There was no restriction on the type of study that was included, publication date and language of publication or inclusion of abstracts. Any article with involvement of the specified age group taking at least a single dose of azithromycin was assessed. Only articles with information on the safety of azithromycin were included, such as any mention of an adverse drug reaction, drug toxicity, drug, side effects or adverse event.

Data quality assessment

The Randomized controlled trials (RCTs) were assessed using the Cochrane collaboration's tool for assessing risk of bias [19] by two independent reviewers (Figure 1). Studies with low risk of bias in at least four of the six parameters were included in the meta-analysis.

Data collection and statistical analysis

A single reviewer undertook eligibility assessment. Each title and available abstract was screened for appropriateness and relevant articles obtained. Articles were examined independently by a second reviewer to confirm they met inclusion criteria. Hand searching of references of articles was done. Data were extracted from relevant articles on methodology, characteristics of trial participants (including condition and gestational age), number of neonates receiving azithromycin, number of participants in study, route of

administration, dose, duration of azithromycin treatment, comparator drugs and adverse events.

Meta-analysis was carried out in Revman version 5.3. Relative risks and 95% confidence intervals were estimated for each RCT. Overall relative risks were calculated from the RCTs. Begg and Mazumdar's rank correlation tests were used to assess publication bias. No significant publication bias was found. Between studies heterogeneity was assessed using a Chi-squared test where a p-value less than 0.05 indicated significant heterogeneity. Fixed effect models were used to produce summary relative risks and 95% confidence intervals where heterogeneity did not exist. If statistical heterogeneity did exist then random effects models were applied.

RESULTS

A total of 11 articles involving 473 neonates were identified (Figure 2). The majority of the studies (4 studies) were RCTs. There were 3 pharmacokinetic studies and 3 cohort studies (Table 1). One case report was identified. The RCTs involved 211 neonates who received azithromycin and 198 controls. The cohort studies and PK studies involved 218 and 43 neonates respectively. Three hundred and seventy one AEs were reported. Adverse events were mainly respiratory (358/1000 neonate), neurological (273/1000 neonates), and gastrointestinal (196/1000 neonates) in origin. Vomiting (44/1000 neonates), diarrhoea (15/1000 neonates) abdominal tenderness (22/1000 neonates) and feeding intolerance (37/1000 neonates) were the most frequently reported gastrointestinal symptoms. The majority of the respiratory and neurological AEs were prematurity related (Table 2).

Evidence from RCTs

Two of the 4 RCTs were placebo controlled. 10mg/kg/d of intravenous azithromycin was administered for one week followed by a 5 week course of 5mg/kg/d as prophylaxis for BPD in both studies. [20,21] A third study administered 5mg/kg/d for 1 week after an initial 1 week course of oral 10mg/kg/d. [22] The patients in the comparator arm of this study were not given any treatment. Meta-analysis of the incidence of BPD between neonates

administered azithromycin and the control group in the three studies showed that azithromycin significantly reduced the risk of BPD in extremely premature neonates [RR=0.83, 95% CI: 0.71-0.98, p=0.02] (Figure 3). While 55% of preterm neonates given azithromycin developed BPD compared to 67% of those without treatment or given placebo. Funnel plot of these RCTs show no publication bias (Figure 4). The fourth study compared the efficacy of azithromycin with erythromycin for the treatment of chlamydia conjunctivitis. [23] Ninety-six percent of children treated with 3 days intravenous 10mg/kg and subsequent 4 days oral dose azithromycin recovered compared with 76% of those given twice daily 10mg/kg erythromycin for 3 days followed by 11 days of thrice daily oral erythromycin. A significantly higher cure rate (p=0.03) was achieved with azithromycin than erythromycin.

There was no significant difference in the incidence of elevated liver enzymes between azithromycin and placebo group (p=0.76) (Figure 5). All cases of elevated transaminases (16 cases) were reported in a single RCT.[20] There were 13 cases of elevated transaminases in the control group of this study. Only one placebo/no treatment controlled trial reported vomiting as an adverse event, with no significant difference between the azithromycin group and the neonates without treatment (p=0.79). The other AEs reported in the placebo/no treatment controlled RCTs were prematurity related (intraventricular haemorrhage, periventricular leucomalacia, necrotizing enterocolitis, patent ductus arteriosus and hearing abnormalities) and there were no significant differences between azithromycin and the comparator arms. [20-22] A Chinese study reported more cases of diarrhoea, abdominal pain and reduced appetite in the children treated with oral erythromycin (after 3 days of IV treatment), compared with those administered azithromycin.[23]

Evidence from observational studies

Two cohort studies were identified. One of these studies involved a cohort of neonates given either azithromycin or erythromycin following exposure to a patient with pertussis.[24] Fifty eight neonates received azithromycin while 18 were given erythromycin. None of the neonates developed IHPS. Fourteen (24%) of those given azithromycin experienced AEs. These included 3 cases each of irritability, candidiasis and vomiting; 2 cases of rash and one case each of diarrhoea, abdominal pain and blood in the stool Ten

(56%) of the neonates given erythromycin experienced AEs. There was a significantly lower incidence of diarrhoea (p=0.01) in the azithromycin treated compared with erythromycin treated neonates. The incidences of other AEs were not significantly different.

The second observational study involved twelve neonates who received varying doses of azithromycin suspension for the treatment of chlamydia conjunctivitis.[25] Three of the 5 neonates (60%) administered a single dose of 20mg/kg became culture negative; while 6 of the 7 (86%) given 20mg/kg/d for three days became culture negative. No AEs were reported in this study

Retrospective study

A single retrospective cohort study was identified. This study explored the risk of infantile hypertrophic pyloric stenosis (IHPS) in neonates exposed to azithromycin and erythromycin, using the United States military health system (MHS) database. Of the one hundred and forty eight neonates (0-14 days old) treated with azithromycin, 3 (2%) developed IHPS. Nine (3%) of the 291 neonates (0-14 days) given erythromycin had IHPS.[26]

Pharmacokinetic studies

A single dose 20mg/kg was administered in a pharmacokinetic study[27] and 10mg/kg single dose administered in two other pharmacokinetic studies.[28,29] All the AEs reported in two these studies were prematurity related and none was attributed to azithromycin. [27, 28] There were 4 cases of intraventricular haemorrhage, 3 of hearing loss, 2 of necrotising enterocolitis, 1 each of periventricular leucomalacia, respiratory distress syndrome, pneumomediastinum and hyperbilirubinemia. No AEs were observed in the third study.[29]

Case report

There was one case report of pyloric stenosis in a 5 week old infant who had received 5 days of oral azithromycin at 3 weeks of life as treatment for chlamydia conjunctivitis. [30]

DISCUSSION

Only a small population of neonates have been treated with azithromycin and no major AE has been documented. This systematic review shows that azithromycin significantly reduces the risk of BPD in neonates and is also effective in the treatment of chlamydia conjunctivitis. A previous systematic review has also demonstrated the efficacy of azithromycin, in the prevention of BPD.[31] Macrolide antibiotics are inhibitors of Ureaplasma. The relationship between Ureaplasma infection and BPD has been explored with varying outcomes reported from different studies. [15, 17, 32] We have also identified two off-label studies demonstrating the efficacy of azithromycin against chlamydia trachomatis in neonates. Previous studies have reported the susceptibility of chlamydia to azithromycin.[33] The dose and duration of treatment with azithromycin varied across the studies. This may be due to its off-label use and the absence of a standardised dosing regimen for the drug in this age group.

The majority of the AEs reported in preterm neonates were related to prematurity and were unlikely to be caused by azithromycin. Results from one of the studies however showed that azithromycin had a better safety profile than erythromycin in neonates. Diarrhoea, abdominal discomfort and reduced appetite were less frequent in azithromycin treated neonates. In another study, 2% and 3% respectively, of neonates exposed to azithromycin and erythromycin within 14 days of life developed IHPS.[26] Both erythromycin and azithromycin are gastric motilin receptor agonists.[34] Activation of these receptors by erythromycin with consequent increased pyloric contractions has been hypothesised as a possible cause pyloric hypertrophy in neonates.[35] The association between erythromycin and pyloric stenosis has been demonstrated in previous studies. High dose, and early neonatal exposure to the drug within the first 14 days of life are known risk factors. [36] Post-natal exposure to macrolides from breast milk has also been associated with IHPS. [37] Further studies are required to determine the relationship between neonatal azithromycin use and IHPS.

Although arrhythmias had been reported in azithromycin treated adults; [38, 39] none of the reviewed studies evaluated neonates for arrhythmia. There is a documented case of arrhythmia in an infant following azithromycin overdose [40] and spiramycin, which is a structurally similar macrolide, has been associated with neonatal arrhythmia. [41]

In conclusion, azithromycin significantly reduces the risk of BPD in preterm neonates and it is effective for the treatment of chlamydia conjunctivitis. It has a better safety profile than erythromycin in the limited number of treated neonates. The relationship between azithromycin and IHPS requires further investigation.

Table 1: Summary of all included studies

Reference	Study type	Comparator	No of patients AZT	No of patients control	Number of AEs	AZT dose	Indication	Country
Ballard et al (2011)[20]	RCT	Placebo	111	109	231	10mg/kg x 1wk then 5mg/kg/d x 5wks (IV)	BPD	USA
Ballard et al (2007)[21]	RCT	Placebo	19	16	39	10mg/kg x 1wk then 5mg/kg/d x 5wks (IV)	BPD	USA
Gharehbaghi et al (2011)[22]	RCT	Nil	56	52	52	10mg/kg x 1wk then 5mg/kg/d x 1wk (oral)	BPD	Iran
Dong (2005)[23]	RCT	Erythromycin	25	21	18	10mg/kg x3 days(IV) then 4 days without treatment then 10mg/kg x3 days (oral)	Chlamydia	China
Friedman et al (2004)[24]	Cohort	-	58	-	13	10-12mg/kg x 5 days (oral)	Pertussis	USA
Hammerschlag et al (1998)[25]	Cohort	-	12	-	0	20mg/kg single dose and 20mg/kg/d x 3 days (oral)	Chlamydia	USA
Eberly et al (2015)[26]	Cohort	-	148	-	3	NA	-	USA
Viscardi et al (2013)[26]	Pharmacokinetic	-	13	-	7	20mg/kg once	U. Urealyticum	USA
Hassan et al (2010)[27]	Pharmacokinetic	-	14	-	10	10mg/kg once	BPD	USA
Tessema et al (2007)[28]	Pharmacokinetic	-	16	-	0	10mg/kg once	-	USA
Zayas et al (2010)[29]	Case report	-	1	-	1	NA	Chlamydia	USA

Table 2: Classification and risk of adverse events from RCTs and observational studies (n=324)

Classification	Adverse Event	Number	Risk of AE per 1000 neonates	95% CI
Gastrointestinal	Vomiting	12	37	21-64
	Feeding intolerance/poor feeding	10	31	16-57
	NEC	8	25	12-49
	Abdominal tenderness	6	19	8-41
	Diarrhoea	4	12	5-33
	Other gastrointestinal symptoms	13	40	24-68
		53	**163**	**128-209**
Respiratory	BPD	96	296	251-350
	Respiratory distress	1	3	4-22
		97	**299**	**253-354**
CNS	At least grade 3 IVH	29	90	63-127
	Abnormal hearing	22	68	45-102
	PVL	15	46	28-76
	Others	4	12	5-33
		74	**228**	**187-279**
Hepatobiliary	Elevated transaminase	**16**	**49**	**31-80**
Cardiovascular	PDA	**20**	**62**	**40-94**
Metabolic	Hyperkalaemia	**2**	**6**	**2-25**
Others	Sepsis	11	34	19-61
	Other infections	96	296	251-350
	Allergy	2	6	2-25
Total		**371**		

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CONTIBUTORSHIP

IC, SK, EJ, and HS conceived the idea; CS performed the literature search and extracted the data. OE updated the search and verified the extracted data. OE produced the first draft of the manuscript. All authors contributed to the subsequent and final drafts of the manuscript.

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COMPETING INTEREST: No, there are no competing interests.

DATA SHARING: No additional data available.

Image legend

Figure 1: Summary of risk of bias

Figure 2: Flow chart of included articles

Figure 3: Relative risks of BPD in azithromycin and untreated/placebo treated preterm neonates.

Figure 4: Funnel plot to determine publication bias

Figure 5: Relative risk of elevated transaminase in azithromycin and placebo treated neonates.

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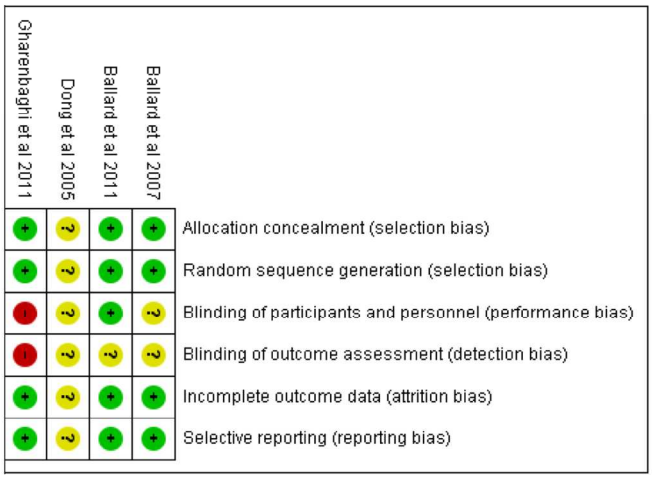

Summary of risk of bias
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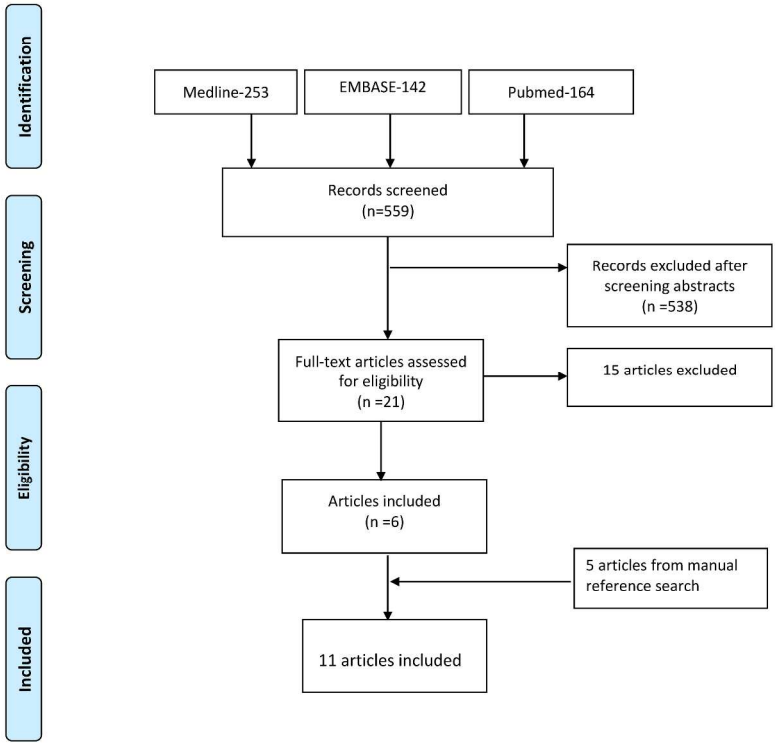

Flow chart of included articles
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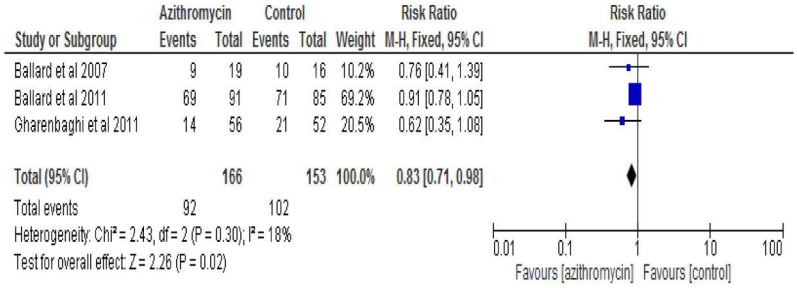

Relative risks of BPD in azithromycin and untreated/placebo treated preterm neonates.
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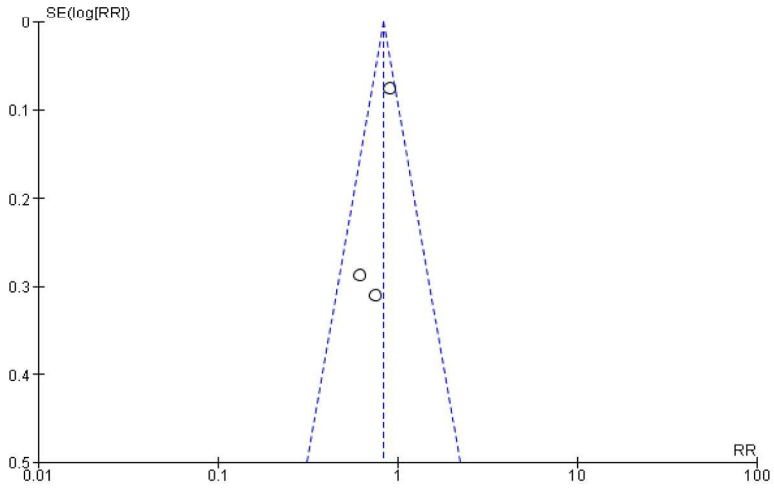
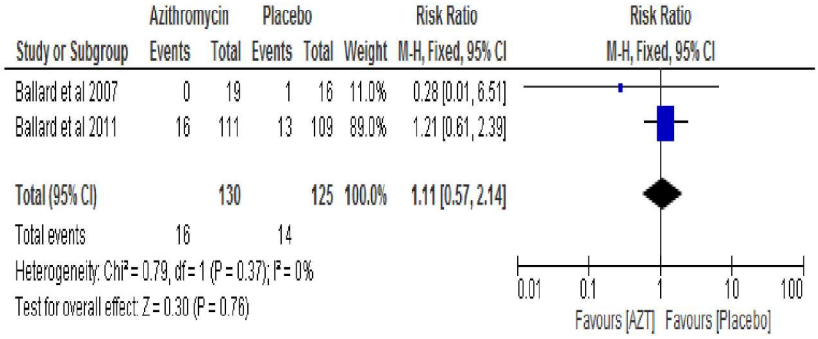


Funnel plot to determine publication bias
209x148mm (300 x 300 DPI)



Relative risk of elevated transaminase in azithromycin and placebo treated neonates.
297x210mm (300 x 300 DPI)

PRISMA Checklist: USE AND SAFETY OF AZITHROMYCIN IN NEONATES: SYSTEMATIC REVIEW

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	p1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	p2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	P4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	p4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	P5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	P5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	P5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	p5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	p5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	p5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	P6

PRISMA Checklist: USE AND SAFETY OF AZITHROMYCIN IN NEONATES: SYSTEMATIC REVIEW

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	P6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not applicable
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Figure 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 3&5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	p7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	P9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	P9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P9
FUNDING			

PRISMA Checklist: USE AND SAFETY OF AZITHROMYCIN IN NEONATES: SYSTEMATIC REVIEW

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	P13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Use and safety of azithromycin in neonates: a systematic review

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Keywords:	CLINICAL PHARMACOLOGY, NEONATOLOGY, Adverse events < THERAPEUTICS

USE AND SAFETY OF AZITHROMYCIN IN NEONATES: A SYSTEMATIC REVIEW

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Keywords – Azithromycin, safety, neonates, adverse events

Word count: 2001

ABSTRACT

Objectives: To identify the use and adverse drug reactions associated with azithromycin in neonates.

Setting: Databases MEDLINE (1948–August 2015), EMBASE (1980 – August 2015), and Pubmed (August 2015) were searched for studies on azithromycin in neonates.

Participants: All studies involving neonates (<28 days old) who have received at least a single dose of azithromycin for which safety was evaluated.

Primary and secondary outcome measures: The primary outcome was adverse event (AE) of azithromycin. Use of azithromycin in neonates was the secondary outcome.

Results: A total of 11 articles involving 473 neonates were identified. Three hundred and seventy one AEs were reported. Adverse events were mainly respiratory (358/1000 neonate), neurological (273/1000 neonates), and gastrointestinal (196/1000 neonates) in origin. Azithromycin significantly reduced the risk of bronchopulmonary dysplasia in extremely premature neonates [RR=0.83, 95% CI: 0.71-0.98, p=0.02]. There was no significant difference in the incidence of elevated liver enzymes between azithromycin and placebo group (p=0.76). There were 4 cases of infantile hypertrophic pyloric stenosis (IHPS).

Conclusions: Azithromycin significantly reduces the risk of BPD in preterm neonates. The relationship between azithromycin and IHPS requires further investigation.

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. This systematic review assessed the quality of all the RCTs
2. Randomised controlled trials (RCTs), cohort studies and case reports were reviewed.
3. Only a few studies of azithromycin in neonates have been published.

INTRODUCTION

Azithromycin is a macrolide derivative of erythromycin. It is one of the most commonly prescribed antibiotics in children, with a prescription rate of between 4-14%.[1-3] Since its approval in the USA and Europe,[4,5] it has been used extensively for the treatment of several paediatric infectious diseases. [6] Prescription rate for respiratory tract infection in children is increasing.[3]

Due to lack of efficacy and safety studies, oral and intravenous formulations are not recommended for children less than 6 months[7] and 16 years,[8] respectively. The safety of azithromycin eye drops in children under one year is also unknown.[9,10] Gastrointestinal disorders such as diarrhoea, vomiting and abdominal pain are the most commonly reported side effects in paediatrics.[11] Increased risk of arrhythmia and cardiovascular related death in adults has been reported.[12, 13]

The potential of azithromycin as a chemoprophylactic agent for Bronchopulmonary Dysplasia (BPD) in neonates is still under exploration. Ureaplasma infection, which has been shown to be susceptible to the drug,[14,15] is associated with BPD.[16,17] Despite limited efficacy and safety data, the US Centre for Disease Control (CDC) considers azithromycin as the first choice treatment and chemoprophylaxis of choice for pertussis in neonates. Treatment is recommended for 5-7 days[18]

There is currently insufficient information on azithromycin treatment in neonates; therefore, this systematic review aims to evaluate all published data and reports on the safety and use of the drug in this age group.

METHODS

This review was done as per PRISMA guideline. The systematic review protocol was not published.

Search strategy

The databases MEDLINE (1948 – August 2015), EMBASE (1980 – August 2015), and Pubmed (up to August 2015) were searched. Search words: 'preterm or neonat* or neonate* or newborn* or infan*' in title and abstract were combined with 'azithromycin' in title and abstract for all databases. Manual search of bibliography was also done.

Eligibility criteria

Any published literature with documented involvement of neonates (birth-28 days) administered azithromycin via any route of administration for any disease condition. There was no restriction on the type of study that was included, publication date and language of publication or inclusion of abstracts. Any article with involvement of the specified age group taking at least a single dose of azithromycin was assessed. Only articles with information on the safety of azithromycin were included, such as any mention of an adverse drug reaction, drug toxicity, drug, side effects or adverse event.

Data quality assessment

The Randomized controlled trials (RCTs) were assessed using the Cochrane collaboration's tool for assessing risk of bias [19] by two independent reviewers (Figure 1). Studies with low risk of bias in at least four of the six parameters were included in the meta-analysis.

Data collection and statistical analysis

A single reviewer undertook eligibility assessment. Each title and available abstract was screened for appropriateness and relevant articles obtained. Articles were examined independently by a second reviewer to confirm they met inclusion criteria. Hand searching of references of articles was done. Data were extracted from relevant articles on methodology, characteristics of trial participants (including condition and gestational age),

number of neonates receiving azithromycin, number of participants in study, route of administration, dose, duration of azithromycin treatment, comparator drugs and adverse events.

Meta-analysis was carried out in Revman version 5.3. Relative risks and 95% confidence intervals were estimated for each RCT. Overall relative risks were calculated from the RCTs. Begg and Mazumdar's rank correlation tests were used to assess publication bias. No significant publication bias was found. Between studies heterogeneity was assessed using a Chi-squared test where a p-value less than 0.05 indicated significant heterogeneity. Fixed effect models were used to produce summary relative risks and 95% confidence intervals where heterogeneity did not exist. If statistical heterogeneity did exist then random effects models were applied.

RESULTS

A total of 11 articles involving 473 neonates were identified (Figure 2). The majority of the studies (4 studies) were RCTs. There were 3 pharmacokinetic studies and 3 cohort studies (Table 1). One case report was identified. The RCTs involved 211 neonates who received azithromycin and 198 controls. The cohort studies and PK studies involved 218 and 43 neonates respectively. Three hundred and seventy one AEs were reported. Adverse events were mainly respiratory (358/1000 neonate), neurological (273/1000 neonates), and gastrointestinal (196/1000 neonates) in origin. Vomiting (44/1000 neonates), diarrhoea (15/1000 neonates) abdominal tenderness (22/1000 neonates) and feeding intolerance (37/1000 neonates) were the most frequently reported gastrointestinal symptoms. The majority of the respiratory and neurological AEs were usually associated with prematurity (Table 2).

Evidence from RCTs

Two of the 4 RCTs were placebo controlled. 10mg/kg/d of intravenous azithromycin was administered for one week followed by a 5 week course of 5mg/kg/d as prophylaxis for BPD in both studies. [20,21] A third study administered 5mg/kg/d for 1 week after an initial 1

week course of oral 10mg/kg/d. [22] The patients in the comparator arm of this study were not given any treatment. Meta-analysis of the incidence of BPD between neonates administered azithromycin and the control group in the three studies showed that azithromycin significantly reduced the risk of BPD in extremely premature neonates [RR=0.83, 95% CI: 0.71-0.98, p=0.02] (Figure 3). While 55% of preterm neonates given azithromycin developed BPD compared to 67% of those without treatment or given placebo. Funnel plot of these RCTs show no publication bias (Figure 4). The fourth study compared the efficacy of azithromycin with erythromycin for the treatment of chlamydia conjunctivitis. [23] Ninety-six percent of children treated with 3 days intravenous 10mg/kg and subsequent 4 days oral dose azithromycin recovered compared with 76% of those given twice daily 10mg/kg erythromycin for 3 days followed by 11 days of thrice daily oral erythromycin. A significantly higher cure rate (p=0.03) was achieved with azithromycin than erythromycin.

There was no significant difference in the incidence of elevated liver enzymes between azithromycin and placebo group (p=0.76) (Figure 5). All cases of elevated transaminases (16 cases) were reported in a single RCT.[20] There were 13 cases of elevated transaminases in the control group of this study. Only one placebo/no treatment controlled trial reported vomiting as an adverse event, with no significant difference between the azithromycin group and the neonates without treatment (p=0.79). The other AEs reported in the placebo/no treatment controlled RCTs were usually associated with prematurity (intraventricular haemorrhage, periventricular leucomalacia, necrotizing enterocolitis, patent ductus arteriosus and hearing abnormalities) and there were no significant differences between azithromycin and the comparator arms. [20-22] A Chinese study reported more cases of diarrhoea, abdominal pain and reduced appetite in the children treated with oral erythromycin (after 3 days of IV treatment), compared with those administered azithromycin.[23]

Evidence from observational studies

Two cohort studies were identified. One of these studies involved a cohort of neonates given either azithromycin or erythromycin following exposure to a patient with pertussis.[24] Fifty eight neonates received azithromycin while 18 were given erythromycin. None of the neonates developed IHPS. Fourteen (24%) of those given azithromycin

experienced AEs. These included 3 cases each of irritability, candidiasis and vomiting; 2 cases of rash and one case each of diarrhoea, abdominal pain and blood in the stool Ten (56%) of the neonates given erythromycin experienced AEs. There was a significantly lower incidence of diarrhoea (p=0.01) in the azithromycin treated compared with erythromycin treated neonates. The incidences of other AEs were not significantly different.

The second observational study involved twelve neonates who received varying doses of azithromycin suspension for the treatment of chlamydia conjunctivitis.[25] Three of the 5 neonates (60%) administered a single dose of 20mg/kg became culture negative; while 6 of the 7 (86%) given 20mg/kg/d for three days became culture negative. No AEs were reported in this study

Retrospective study

A single retrospective cohort study was identified. This study explored the risk of infantile hypertrophic pyloric stenosis (IHPS) in neonates exposed to azithromycin and erythromycin, using the United States military health system (MHS) database. Of the one hundred and forty eight neonates (0-14 days old) treated with azithromycin, 3 (2%) developed IHPS. Nine (3%) of the 291 neonates (0-14 days) given erythromycin had IHPS.[26]

Pharmacokinetic studies

A single dose 20mg/kg was administered in a pharmacokinetic study[27] and 10mg/kg single dose administered in two other pharmacokinetic studies.[28,29] All the AEs reported in two these studies were usually associated with prematurity and none was attributed to azithromycin. [27, 28] There were 4 cases of intraventricular haemorrhage, 3 of hearing loss, 2 of necrotising enterocolitis, 1 each of periventricular leucomalacia, respiratory distress syndrome, pneumomediastinum and hyperbilirubinemia. No AEs were observed in the third study.[29]

Case report

There was one case report of pyloric stenosis in a 5 week old infant who had received 5 days of oral azithromycin at 3 weeks of life as treatment for chlamydia conjunctivitis. [30]

DISCUSSION

Only a small population of neonates have been treated with azithromycin and no major AE has been documented. This systematic review shows that azithromycin significantly reduces the risk of BPD in neonates and is also effective in the treatment of chlamydia conjunctivitis. A previous systematic review has also demonstrated the efficacy of azithromycin, in the prevention of BPD.[31] Macrolide antibiotics are inhibitors of Ureaplasma. The relationship between Ureaplasma infection and BPD has been explored with varying outcomes reported from different studies. [15, 17, 32] We have also identified two off-label studies demonstrating the efficacy of azithromycin against chlamydia trachomatis in neonates. Previous studies have reported the susceptibility of chlamydia to azithromycin.[33] Azithromycin was administered once daily in all studies because of its long half-life, which is estimated to be between 26- 83 hours in neonates.[25] The dose and duration of treatment with azithromycin varied across the studies. This may be due to its off-label use and the absence of a standardised dosing regimen for the drug in this age group. Very few studies have been conducted in neonates; hence the safety and efficacy of different dosing regimen for different indications have not been established.

The majority of the AEs reported in preterm neonates were related to prematurity and were unlikely to be caused by azithromycin. Results from one of the studies however showed that azithromycin had a better safety profile than erythromycin in neonates. Diarrhoea, abdominal discomfort and reduced appetite were less frequent in azithromycin treated neonates. In another study, 2% and 3% respectively, of neonates exposed to azithromycin and erythromycin within 14 days of life developed IHPS.[26] Both erythromycin and azithromycin are gastric motilin receptor agonists.[34] Activation of these receptors by erythromycin with consequent increased pyloric contractions has been hypothesised as a possible cause pyloric hypertrophy in neonates.[35] The association between erythromycin and pyloric stenosis has been demonstrated in previous studies. High dose, and early neonatal exposure to the drug within the first 14 days of life are known risk factors. [36] Azithromycin, like erythromycin, binds to and activates the motilin receptors.[37]

Erythromycin is however believed to have a stronger gastrointestinal prokinetic effect than azithromycin.[38] These drugs are slightly structurally different, with erythromycin having a 14-C member heterocyclic ring and azithromycin a 15 member ring.[39] The effect of the structural differences on motilin receptor binding and IHPS requires further exploration. Post-natal exposure to macrolides from breast milk has also been associated with IHPS. [40] Further studies are required to determine the relationship between neonatal azithromycin use and IHPS.

Although prolonged QT_c interval and torsades de pointes had been reported in azithromycin treated adults; [41] none of the reviewed studies evaluated neonates for arrhythmia. There is a documented case of arrhythmia in an infant following azithromycin overdose [42] and spiramycin, which is a structurally similar macrolide, has been associated with neonatal arrhythmia. [43] Prolonged QT_c interval can be normal in the first few days of life in premature neonates, hence it is difficult to identify drug induced aetiology during this period [44].

In conclusion, azithromycin significantly reduces the risk of BPD in preterm neonates and it is effective for the treatment of chlamydia conjunctivitis. It has a better safety profile than erythromycin in the limited number of treated neonates. The relationship between azithromycin and IHPS requires further investigation. More studies are required to determine a safe and effective dose for azithromycin in neonates.

Table 1: Summary of all studies involving term and preterm neonates

Reference	Study type	Comparator	Age (days)	No of patients AZT	No of patients control	Number of AEs	AZT dose	Indication	Country
ǂBallard et al (2011)[20]	RCT	Placebo	<3	111	109	231	10mg/kg x 1wk then 5mg/kg/d x 5wks (IV)	BPD	USA
ǂBallard et al (2007)[21]	RCT	Placebo	<3	19	16	39	10mg/kg x 1wk then 5mg/kg/d x 5wks (IV)	BPD	USA
ǂGharehbaghi et al (2011)[22]	RCT	Nil	<28	56	52	52	10mg/kg x 1wk then 5mg/kg/d x 1wk (oral)	BPD	Iran
Dong (2005)[23]	RCT	Erythromycin	<28	25	21	18	10mg/kg x3 days(IV) then 4 days without treatment then 10mg/kg x3 days (oral)	Chlamydia	China
Friedman et al (2004)[24]	Cohort	-	<28	58	-	13	10-12mg/kg x 5 days (oral)	Pertussis	USA
Hammerschlag et al (1998)[25]	Cohort	-	<28	12	-	0	20mg/kg single dose and 20mg/kg/d x 3 days (oral)	Chlamydia	USA
Eberly et al (2015)[26]	Cohort	-	<28	148	-	3	NA	-	USA
ǂViscardi et al (2013)[26]	Pharmacokinetic	-	<3	13	-	7	20mg/kg once	Ureaplasma	USA
ǂHassan et al (2010)[27]	Pharmacokinetic	-	<28	14	-	10	10mg/kg once	BPD	USA
ǂTessema et al (2007)[28]	Pharmacokinetic	-	<28	16	-	0	10mg/kg once	-	USA
ǂZayas et al (2010)[29]	Case report	-	21	1	-	1	NA	Chlamydia	USA

preterm neonates

Table 2: Classification and risk of adverse events from RCTs and observational studies (n=324)

Classification	Adverse Event	Number	Risk of AE per 1000 neonates	95% CI
Gastrointestinal	Vomiting	12	37	21-64
	Feeding intolerance/poor feeding	10	31	16-57
	NEC	8	25	12-49
	Abdominal tenderness	6	19	8-41
	Diarrhoea	4	12	5-33
	Other gastrointestinal symptoms	13	40	24-68
		53	**163**	**128-209**
Respiratory	BPD	96	296	251-350
	Respiratory distress	1	3	4-22
		97	**299**	**253-354**
CNS	At least grade 3 IVH	29	90	63-127
	Abnormal hearing	22	68	45-102
	PVL	15	46	28-76
	Others	4	12	5-33
		74	**228**	**187-279**
Hepatobiliary	Elevated transaminase	**16**	**49**	**31-80**
Cardiovascular	PDA	**20**	**62**	**40-94**
Metabolic	Hyperkalaemia	**2**	**6**	**2-25**
Others	Sepsis	11	34	19-61
	Other infections	96	296	251-350
	Allergy	2	6	2-25
Total		**371**		

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CONTIBUTORSHIP

IC, SK, EJ, and HS conceived the idea; CS performed the literature search and extracted the data. OE updated the search and verified the extracted data. OE produced the first draft of the manuscript. All authors contributed to the subsequent and final drafts of the manuscript.

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Competing interest: No, there are no competing interests.

Data sharing: No additional data available.

Image legend

Figure 1: Summary of risk of bias

Figure 2: Flow chart of included articles

Figure 3: Relative risks of BPD in azithromycin and untreated/placebo treated preterm neonates.

Figure 4: Funnel plot to determine publication bias

Figure 5: Relative risk of elevated transaminase in azithromycin and placebo treated neonates.

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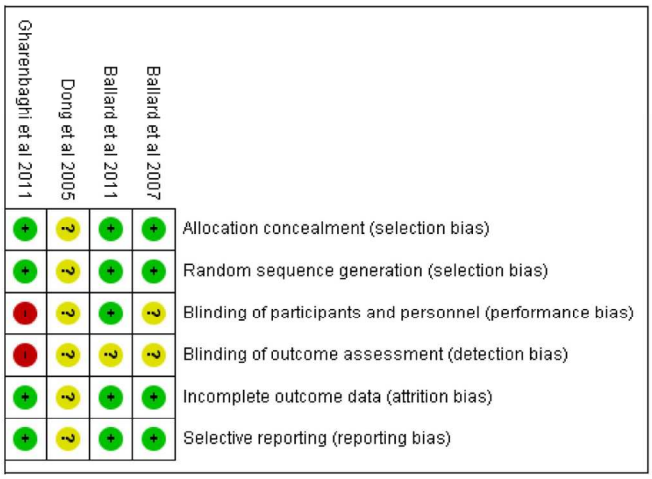

Summary of risk of bias
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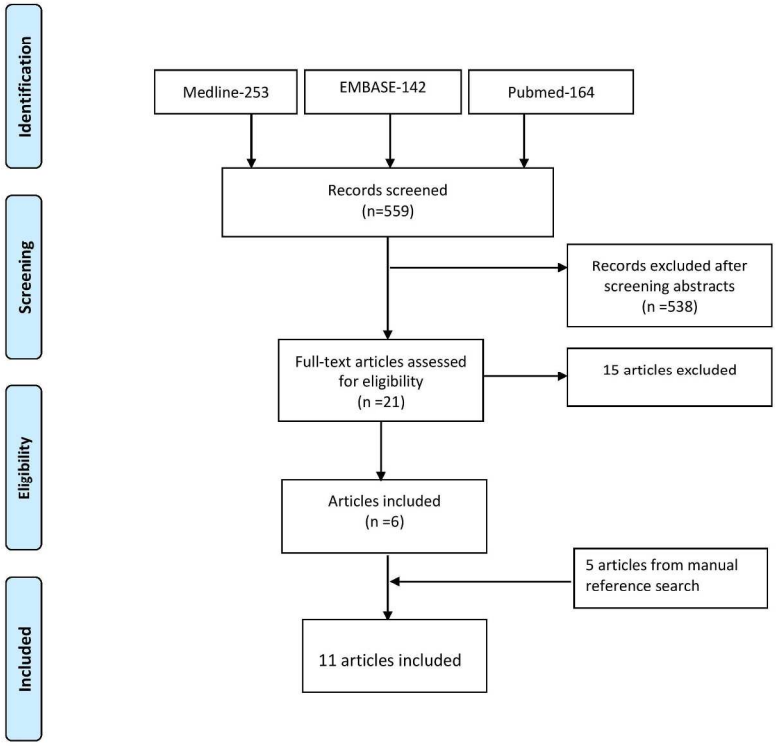

Flow chart of included articles
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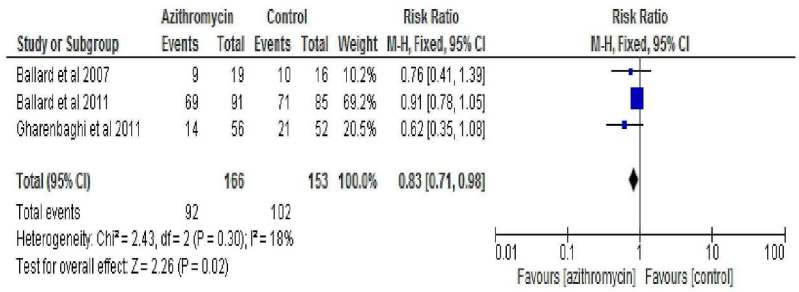

Relative risks of BPD in azithromycin and untreated/placebo treated preterm neonates.
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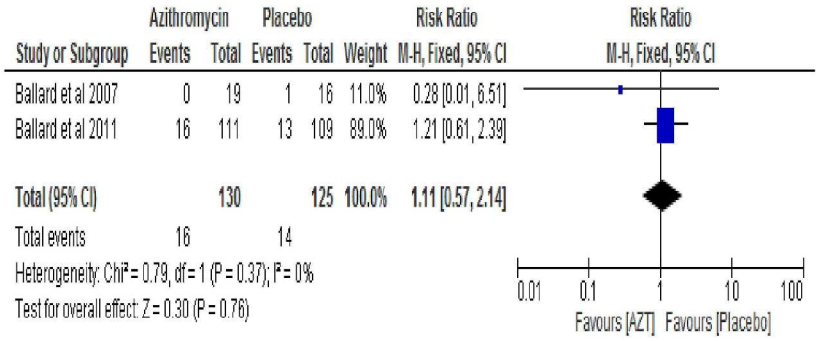

Relative risk of elevated transaminase in azithromycin and placebo treated neonates.
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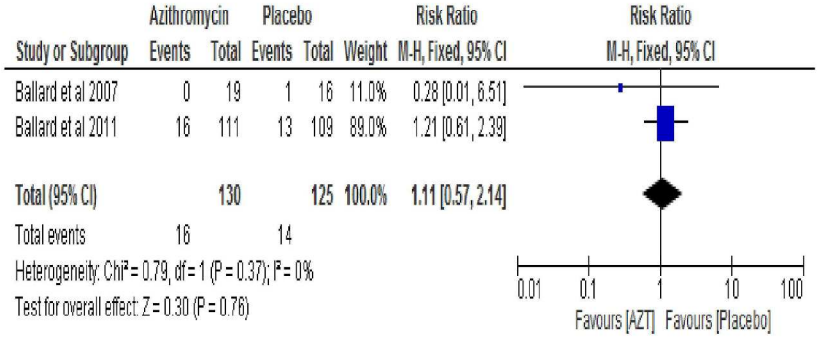

Relative risk of elevated transaminase in azithromycin and placebo treated neonates.
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PRISMA Checklist: USE AND SAFETY OF AZITHROMYCIN IN NEONATES: SYSTEMATIC REVIEW

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	p1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	p2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	P4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	p4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	P5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	P5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	P5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	p5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	p5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	p5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	P6

PRISMA Checklist: USE AND SAFETY OF AZITHROMYCIN IN NEONATES: SYSTEMATIC REVIEW

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	P6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not applicable
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Figure 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 3&5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	p7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	P9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	P9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P9
FUNDING			

PRISMA Checklist: USE AND SAFETY OF AZITHROMYCIN IN NEONATES: SYSTEMATIC REVIEW

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	P13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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