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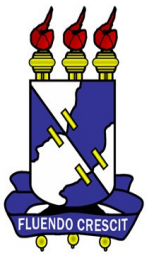


MARINA SANTANA FREIRE

# USO DE ANTAGONISTAS DO RECEPTOR DE HISTAMINA 2 EM NEONATOS: INFECÇÃO, ENTEROCOLITE NECROTIZANTE OU MORTE

Aracaju/SE

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Monografia apresentada à Universidade Federal de Sergipe como requisito parcial à conclusão do curso de Medicina do Centro de Ciências Biológicas e da Saúde.

Orientador: Prof. Dr. Ricardo Queiroz Gurgel

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Aracaju, _____/_____/_____

Autor: Marina Santana Freire

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Aprovada em ____/____/_____

Orientador: Prof. Ricardo Queiroz Gurgel
Universidade Federal de Sergipe

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# AGRADECIMENTOS

Agradeço primeiramente a Deus.

Agradeço a meu orientador Dr. Ricardo Gurgel por todo o apoio e inspiração para a conclusão desse e de outros trabalhos.

Agradeço aos professores Victor S. Santos e a Paulo Ricardo S. Martins Filho por todos os ensinamentos que foram cruciais para a elaboração desse trabalho.

Agradeço a todos que direta ou indiretamente ajudaram para que eu alcançasse mais este objetivo.

# SUMÁRIO

# 1 REVISÃO DE LITERATURA

## 1.1 Introdução

O uso de antagonistas do receptor de histamina-2 (ARH2) é bastante presente no ambiente da Unidade de Terapia Intensiva Neonatal (UTIN). Dentre suas indicações, estão o tratamento empírico da doença do refluxo gastroesofágico (DRGE), profilaxia de úlcera de estresse no pós-operatório, profilaxia de úlcera de estresse em neonatos doentes cujo tubo nasogástrico apresenta sangue quando aspirado e em pacientes recebendo oxigenação extracorpórea (Cothran et al., 1997; Canani et al., 2006).

Assim como muitas drogas utilizadas no manejo de neonatos, os inibidores de secreção gástrica (ISG) são prescritos de maneira *off-label* nessa população pelo aparente benefício e segurança demonstrados em adultos (Terrin et al., 2012; Singh et al., 2016). Vários ensaios clínicos com recém-nascidos a termo e crianças mais velhas mostraram que os antagonistas-H2 melhoraram os sintomas da doença do refluxo gastroesofágico e reduziram a exposição e inflamação esofágica com um perfil de segurança favorável. No entanto, esses resultados ainda não foram reproduzidos em neonatos de muito baixo peso (Romaine, 2016).

Mais recentemente, estudos com pacientes pediátricos têm sinalizado uma relação entre essa classe de drogas e a incidência de infecção, que se torna particularmente preocupante em se tratando de neonatos pelo fato de contribuir diretamente para a principal causa de morbimortalidade desse grupo (Terrin et al., 2012; Bianconi et al., 2007).

Em especial, a relação entre o uso de ARH2 e enterocolite necrotizante (ECN) vem sido estudada em diversos lugares do mundo, dado a alta morbimortalidade dessa doença entre os neonatos. Estima-se que a ECN afete cerca de 7% dos neonatos pesando entre 500 e 1500g e sua taxa de mortalidade seja entre 20-30%, sendo maior em recém-nascidos que necessitem de cirurgia (Neu et al., 2011). Ainda assim, o assunto parece longe de se esgotar, dado em vista os resultados conflitantes advindos desses estudos.

Com o uso indiscriminado dessas medicações no ambiente da Unidade de Terapia Intensiva Neonatal, a necessidade de pesquisas nessa área para a criação de *guidelines* baseados em evidência torna-se imperativa (Barney et al., 2009). Cerca de 8% dos neonatos estão expostos ao uso dessas drogas na UTIN sem existirem protocolos em relação ao seu manejo (Romaine et al., 2005). É necessário elucidar o quanto os ARH2 podem interferir na incidência de infecção, enterocolite necrotizante ou morte para que um uso racional dessas medicações seja instituído.

## 1.2 Neonatos

Após o nascimento, o estabelecimento de uma microbiota intestinal é crucial para manutenção da homeostase. Os neonatos prematuros de baixo peso enfrentam desafios ainda maiores sob esse aspecto. O sistema imunológico e os mecanismos de defesa não-imune mediados podem não estar em pleno funcionamento nesses recém-nascidos, expondo-os à proliferação de patógenos no lúmen e invasão da mucosa intestinal (Bianconi, 2007).

A acidez gástrica é um dos mecanismos de defesa não-imunológicos mais importantes do corpo humano. O suco gástrico contendo ácido clorídrico e pepsina é capaz de matar bactérias em alguns minutos sob um pH < 3 (Conroy et al., 2005; Canani et al., 2006). A falta de estimulação das secreções gástricas e pancreáticas podem contribuir para essa exposição, tal como acontece em neonatos que recebem nutrição parenteral (Neu et al., 2002). Logicamente, a inibição dessa via de defesa através dos inibidores de secreção gástrica (ISG) é capaz de tornar o neonato susceptível à colonização por potenciais patógenos e, consequentemente, levar à infecção (Canani et al., 2006; Terrin et al., 2012).

As infecções hospitalares são as principais complicações em prematuros hospitalizados, podendo provocar aumento no tempo de ventilação mecânica, prolongamento no tempo de internação hospitalar e maior risco de morte (Stoll et al., 1999). Atualmente, é a maior causa de morte dessa população, fato que justifica as inúmeras pesquisas sobre seus fatores de risco, tendo em vista a possibilidade de diminuir cada vez mais os índices de morbimortalidade desses indivíduos (Afjeh et al., 2013).

## 1.3 Antagonistas do receptor de hitamina-2

Algumas condições comuns na UTIN podem contribuir para o desenvolvimento de lesões na mucosa gástrica, como choque séptico, hipotensão, isquemia e algumas drogas como indometacina e corticosteroides, justificando o uso empírico de inibidores de secreção gástrica como os antagonistas do receptor de histamina-2, inibidores de bomba de prótons e sucralfato (Bianconi et al., 2007). Dentre os antagonistas H2 mais utilizados na UTIN estão a ranitidina, cimetidina e famotidina (Romaine et al., 2016). Apesar de a ranitidina não ter seu uso aprovado pelo *Foods and Drug Administration* (FDA) em menores de 1 ano de idade, a administração dessa droga aumentou 7 vezes durante o período de 1999-2004 e 4 vezes de 2000 a 2003 (Afjeh et al., 2013). No entanto, devido aos novos estudos apontando os prováveis riscos dessas medicações, o uso de ARH2 decaiu 23% de 2005 a 2012. Ainda assim, cerca de 8% dos neonatos estão sob exposição dessas drogas (Romaine et al., 2005).

Em adultos, está demonstrado que o uso de ARH2 provoca um aumento do pH gástrico e que isso pode levar à subsequente colonização por cepas de bactérias Gram-negativas a partir de um pH ≥ 4 (Cothran et al., 1997; Kelly et al., 1993). A preocupação com esse evento é o fato de essa colonização contribuir para a incidência de pneumonia nosocomial por Gram-negativos pela aspiração do conteúdo gástrico, além de outras infecções neonatais. Pensando nisso, Cothran et al. (1997) estudaram se a ranitidina seria capaz de elevar o pH ≥ 4 e se esse aumento estaria relacionado com a colonização por bactérias ou fungos em neonatos criticamente doentes. Esse estudo observou que os pacientes recebendo ranitidina obtiveram um pH de 5.6 em média, em comparação com um pH de 4.4 em média do grupo controle. Essa média de pH acima de 4 do grupo controle está explicada pelo fato de que recém-nascidos com menos de 7 dias de vida têm pH gástrico significantemente maior do que em neonatos mais velhos. Em conclusão, foi observado que, apesar de a ranitidina realmente aumentar o pH acima da linha de base e isso favorecer a colonização por bactérias e fungos potencialmente patogênicos, não fora possível determinar se esse evento aumentaria o risco de infecção nosocomial. Kelly et al. (1993) demonstraram que uma pequena dose intravenosa de ranitidina já seria suficiente para elevar o pH acima de 4.

Em um ensaio clínico prospectivo randomizado, Apte et al. (1992) analisaram que houve colonização do trato gastrointestinal (TGI) tanto em neonatos que receberam ranitidina, quanto no grupo controle, porém, no primeiro, acontecia mais precocemente (em média 2 dias vs. 4 dias no grupo controle).

Apesar de um pequeno estudo com 38 neonatos com hemorragia digestiva alta ter mostrado que o sangramento foi controlado mais precocemente no grupo utilizando ranitidina (Sarna et al., 1990), o uso de antagonistas H2 não tem comprovação de benefício em reduzir o dano pulmonar ou as manifestações clínicas da DRGE em neonatos, somado ao fato de não haver efeito positivo no crescimento e desenvolvimento dessas crianças (Afjeh, 2013).

### 1.4 Infecção

As infecções nosocomiais são a maior causa de morte em neonatos admitidos na UTIN. É estimado que o índice de infecções seja de 30% nos pacientes internados nesse setor e corresponde a 40% das mortes em países em desenvolvimento nessa população. Dentre os fatores de risco conhecidos, estão prematuridade, baixo peso ao nascer, uso de dispositivos de pressão positiva contínua nas vias aéreas (CPAP), ventilação mecânica, cateter venoso central, nutrição parenteral e internação prolongada (Rojas et al., 2005; Bianconi et al., 2007; Afjeh et al., 2013). Entretanto, pelos mecanismos das drogas inibidoras de secreção gástrica e por conhecidamente ser um fator de risco para infecções em adultos, é natural que se implique o uso de ISG como um dos fatores predisponentes para infecção em neonatos.

Sharma et al. identificaram uma relação entre o uso de antagonistas H2 e pneumonia associada à ventilação mecânica (2009). No ensaio clínico de Apte et al. (1992), a incidência de pneumonia no grupo ranitidina foi de 81% contra 50% no grupo controle, sendo observado ainda que esse desfecho acontecia mais precocemente nos neonatos em uso da droga. Em 64% dos pacientes que receberam ranitidina e desenvolveram pneumonia, o agente etiológico estava presente no estômago antes de a infecção acontecer. Em 2002, Lopriore et al. compararam a incidência de pneumonia associada a ventilação na UTIN em

pacientes utilizando sucralfato ou ranitidina, porém os resultados foram inconclusivos.

Em 2013, Afjeh et al. observaram que mais de 50% dos neonatos de muito baixo peso (<1.500g) que receberam ranitidina durante cerca de 11 dias desenvolveram infecção nosocomial, concluindo que essa droga seria um fator de risco importante para tal nessa população. Bianconi et al. (2007) concluíram que o uso de ranitidina aumentou em 7 vezes o risco de sepse tardia em neonatos internados na UTIN por pelo menos uma semana. Santana et al. (2017), em um estudo com 300 neonatos, observaram que os usuários de ranitidina estavam mais predispostos da infecção nosocomial, incluindo sepse confirmada e pneumonia. No estudo de Rojas et al. (2005), o risco de infecção nosocomial associado à combinação de uso de corticosteroides com ARH2 foi maior que a soma dos riscos individuais dessas medicações. Esse resultado tinha sido inédito até então e requer mais investigação.

Em contrapartida, Singh et al. (2016) recentemente concluíram em seu estudo com 360 prematuros de muito baixo peso que não houve relação entre o uso de ranitidina e/ou omeprazol e sepse tardia, pneumonia, ECN ou mortalidade. Em relação ao desfecho infecção, o resultado conflitante pode ser justificado pelo fato de que a dose de ranitidina administrada foi maior na população pesquisada por Terrin et al. (2012). Em um estudo prospectivo, Yildizdas et al. (2002) também não encontraram relação entre a incidência de pneumonia associada à ventilação mecânica e o uso de ranitidina, omeprazol ou sucralfato.

### 1.5 Enterocolite Necrotizante

Enterocolite necrotizante afeta de 1 a 3 entre 1.000 nascidos vivos e de 1 a 5% dos neonatos que são admitidos na UTIN. Possui alta taxa de morbimortalidade e é a maior causa da síndrome do intestino curto no período neonatal. Sua etiologia é ainda obscura e seu diagnóstico é difícil, sendo atualmente baseado nos estágios descritos por Bell et al., em 1978, no qual o estágio 1 é definido por achados não específicos e pode incluir intolerância alimentar, distensão abdominal ou os dois. Dentre os critérios para definir o estágio 2, estão os achados radiográficos como pneumatose intestinal, que pode ser difícil de se identificar. Por último, o estágio 3 envolve perfuração de víscera, que pode estar ou não associada à necrose

intestinal e que pode ser espontânea ou advinda do ar da cavidade pleural (Neu et al., 2011).

Dentre os fatores de risco para o desenvolvimento dessa doença, a prematuridade é o principal, somando-se à isquemia intestinal, nutrição enteral e a presença de organismos patogênicos no trato gastrointestinal (Guillet et al., 2006). Devido ao fato de os antagonistas do receptor de histamina-2 favorecerem a proliferação de bactérias no TGI, tem sido bastante estudada a associação entre o uso dessas drogas e a incidência de ECN.

Num estudo retrospectivo de caso—controle, com mais de 11.000 neonatos de muito baixo peso ao nascer, de 1998 a 2001, o tratamento com ARH2 foi associado a uma maior incidência de ECN. O índice dessa patologia correspondeu a 7,1% da população estudada, tendo metade desses pacientes necessitado de cirurgia (Guillet et al., 2006). Na mesma linha de raciocínio, Bilali et al., em 2012, também investigaram essa associação e encontraram aumento no número de casos de ECN nos prematuros em uso de ARH2, mas levando em consideração a presença de outros fatores de risco em potencial como os dados demográficos, clínicos, maternos e o uso de nutrição enteral desses neonatos. O único fator de risco independente para ECN encontrado nesse estudo foi infecção.

Gupta et al. (2013) estudaram a alteração da microflora fecal em neonatos prematuros de muito baixo peso em uso de ARH2 e concluíram que essas drogas são capazes de diminuir a diversidade da microbiota e tendem a favorecer a proliferação de Proteobactérias. Apesar de não avaliar diretamente a incidência de ECN, essas alterações em um TGI imaturo podem favorecer esse desfecho. O uso de ranitidina em prematuros de muito baixo peso (n = 274) provocou um aumento de quase 7 vezes maior de ECN em comparação com o grupo controle (Terrin et al., 2012).

No estudo já citado de Singh et al. (2016), o uso de ranitidina não foi um fator de risco para ECN. Esse resultado em oposição pode ser atribuído ao fato de os estudos de Guillet et al. (2006) e Terrin et al. (2012) não elucidarem o regime nutricional da população estudada, fator de risco conhecido de ECN. Já Guillet et al. (2006) não reportaram a dose e duração da ranitidina. No estudo de Santana et al. (2017), essa droga também não foi relacionada a um aumento da incidência de ECN.

No maior estudo realizado com neonatos de muito baixo peso (n = 127.707), o uso de ARH2 foi fator de risco importante para ECN, infecção e morte. Dentre os 16% dos recém-nascidos que utilizaram antagonistas H2, 32% apresentaram os desfechos de morte, ECN ou sepse. No entanto, apesar de a amostra ser de tamanho impressionante, há limitações admitidas pelo próprio autor, tais como a falta de informação sobre a nutrição dos pacientes e as indicações, posologia e dose de ranitidina utilizados. Também não houve relatos sobre o uso de cateter venoso central, fator de risco conhecido para infecção (Romaine et al., 2016).

### 1.6 Mortalidade

Em adultos, a profilaxia de úlcera de estresse não reduziu significantemente a mortalidade por essa causa. No entanto, o uso de ARH2 tem sido associado a uma taxa de mortalidade mais alta em pacientes em uso de ventilação mecânica quando comparados com aqueles que usaram apenas sucralfato (Tryba et al., 1991). Em neonatos, os estudos ainda não são suficientes para definir essa relação, pois, apesar de muitos artigos sugerirem uma associação entre o uso de ISG e aumento na mortalidade, grande maioria dos recém-nascidos tratados com essas drogas eram doentes graves (Terrin et al., 2012).

Ainda assim, a literatura procura elucidar essa relação. A taxa de mortalidade foi maior nos pacientes que receberam ranitidina do que no grupo controle, porém não foi estatisticamente significante no estudo de Apte et al. (1992). Yildizdas et al. (2002) não encontraram aumento da taxa de mortalidade em pacientes utilizando ranitidina, omeprazol ou sucralfato. Já no estudo de Terrin et al. (2012), os prematuros em uso de ranitidina tiveram uma taxa de mortalidade significantemente mais alta (9,9%) dos que os que não foram expostos à droga (1,6%). Porém, as causas *mortis* não foram esclarecidas, de maneira que, atribuí-las à ranitidina pode ser algo precipitado. Santana et al. (2017) observaram aumento da mortalidade nos neonatos em uso de ranitidina em 4 vezes.

### 1.7 Conclusão

Devido aos resultados conflitantes, especialmente pelos estudos mais recentes, um ensaio clínico randomizado é altamente sugerido para elucidar a

causa dos resultados discordantes e para estabelecer uma associação mais definitiva entre o uso de ARH2 e os desfechos de infecção, enterocolite necrotizante e mortalidade (Singh, 2016).

Uma grande problemática nos estudos que colocam os ARH2 como fator de risco para infecção, enterocolite necrotizante ou morte é o fato de os pacientes estudados já serem criticamente doentes, além de muitos não elucidarem a dose e o tempo de uso das medicações, tornando mais difícil esclarecer o risco-benefício dessas drogas.

Além disso, é preciso que entendamos melhor a fisiopatologia da ECN para que possamos compreender a maneira com que as medicações podem interferir nesse sistema. Assim, saberemos intervir de forma adequada e proteger melhor esses seres tão vulneráveis.

De fato, o uso indiscriminado dessas medicações já está diminuindo devido à segurança em neonatos estar sendo colocada em prova pelos estudos previamente citados. Até que se tenham resultados ainda mais confiáveis, é preciso que o uso de ARH2 seja realmente cauteloso nessa população, restringindo-o aos casos em que o benefício claramente supere o risco.

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4. Figures: Have you uploaded figures separately from the text? Have they been supplied in an acceptable format and are they of sufficient quality? Are they suitable for black and white reproduction (unless you intend to pay any required fees for colour printing)? Have the files been labelled appropriately? Have the figures been cited in the text? Have you provided appropriate figure legends?
5. References: Have all of the references been cited in the text?
6. Supplementary files: Have you supplied these in an acceptable format? Have they been cited in the main text?
7. Statements: Have you included the necessary statements relating to contributorship, competing interests and funding, data sharing, patient consent and ethical approval?
8. Research reporting checklists: Have you either provided the appropriate statement for your study type, or explained why a checklist isn't required?
9. Reproducing figures: Have you obtained permission from the copyright holder to re-use any previously published material? Has the source been acknowledged?

## 2.1 General norms

Editorial policy

*Archives of Disease in Childhood* adheres to the highest standards concerning its editorial policies on publication ethics, scientific misconduct, consent and peer review criteria. To view all BMJ Journal policies please refer to the BMJ Author Hub policies page.

Articles are published under an exclusive licence (or non-exclusive licence for UK Crown and US Federal Government employees) and authors retain copyright. Articles can also be published under a Creative Commons licence to facilitate reuse of the content; please refer to the *Archives of Disease in Childhood* Copyright Author Licence Statement.

Manuscript transfer

BMJ and the Royal College of Paediatrics and Child Health have a facility for transferring manuscripts among their paediatric journals. Authors submitting to the flagship journal *Archives of Disease in Childhood* can choose *BMJ Paediatrics Open* as an 'alternate journal'.

Once authors agree for their manuscript to be transferred to another BMJ journal, all versions of the manuscript, any supplementary files and peer review comments will automatically be transferred on the author's behalf. Please note that there is no guarantee of acceptance. Contact the editorial team for more information or assistance.

Article publishing charges

During submission, authors can choose to have their article published open access for 1950 GBP (exclusive of VAT for UK and EU authors). There are no submission, page or colour figure charges.

For more information on open access, funder compliance and institutional programmes please refer to the BMJ Author Hub open access page.

Paediatric and Perinatal Drug Therapy

Articles for the Paediatric and Perinatal Drug Therapy section should follow the same submission guidelines as the relevant article type, ie, if you are submitting a full original report for the PPDT section it should adhere to the "Original reports" instructions as outlined below.

Submission guidelines

Please review the below article type specifications including the required article lengths, illustrations, table limits and reference counts. The word count excludes the

title page, abstract, tables, acknowledgements, contributions and references. Manuscripts should be as succinct as possible.

For further support when making your submission please refer to the resources available on the BMJ Author Hub. Here you can also find general formatting guidelinesacross BMJ and a formatting checklist.

Original reports

These should report original research. (max 2500 words, excluding abstract, tables and figures and references). The body of the report should be double spaced. The tables should be single spaced and the tables and figures should be at the end of the submission after the references. Please note that all RCT must be appropriately registered and this should be noted on the cover page.

Title

The title should have no more than 10 words. If relevant, the title should include information as to whether the paper is a randomised control trial, meta-analysis, audit, observational study, etc.

Abstract

The abstract of an experimental or observational study must clearly state in sequence and in not more than 250 words (i) the main purpose of the study, (ii) the essential elements of the design of the study, (iii) the most important results illustrated by numerical data but not p values, and (iv) the implications and relevance of the results.

We require a structured abstract of up to 250 words for reports of randomised controlled trials and meta-analyses, and we encourage it for other studies, where appropriate. The following headings should be used for original research:

- Objective
- Design
- Setting
- Patients
- Interventions
- Main outcome measures
- Results: give numerical data rather than vague statements that drug x produced a better response than drug y. Favour confidence intervals over p values, and give the numerical data on which any p value is based.

- Conclusions: do not make any claims that are not supported by data in the paper in the abstract.

Important considerations

- All research reports involving human subjects must contain a statement about ethics committee approval (or equivalent) at the end of the methods section.
- On a separate page (before the references) all original papers should include:
    - “What is already known on this topic” – followed by a maximum of 3 brief statements (no more than 25 words per statement);
    - “What this study adds” – followed by a maximum of 3 brief statements (no more than 25 words per statement).
- Illustrations should be used only when data cannot be expressed clearly in any other way. When graphs are submitted the numerical data on which they are based should be uploaded to ScholarOne as a supplementary file.

Research checklists should be uploaded during the submission process, if these are not applicable to your research please state the reason in your cover letter.

Word count: up to 2500 words (excluding title page, abstract, tables, figures, and references)

Structured abstract: up to 250 words

Tables/Illustrations: up to 5

References: up to 40

Additional material may be considered as data supplements.

Short reports / Case reports

Short reports are brief reports of original research and case reports are any report/case history of four cases or less. ADC only rarely publishes case reports/series and to be successful, the paper must have either exceptional hypothesis generating strength or a powerful and novel clinical message. The abstract of a paper that focuses on a case report(s) must summarise the essential descriptive elements of the case(s) and indicate their relevance and importance. If more illustrations are required, the text must be reduced accordingly. The title should be no longer than seven words. All case reports must be submitted with a scanned patient consent form uploaded as a supplemental file. Please click here for the Patient Consent Form.

Word count: up to 1200 words (excluding title page, abstract, tables, figures, and references)
Abstract: up to 150 words
Tables/Illustrations: up to 2 small tables or images
References: up to 5
Letters to the editor
The editor encourages submissions of important and topical observations or original exploratory research as a letter to the editor.
Word count: up to 500 words
Abstract: not required
Tables/Illustrations: up to 2
References: up to 4
Archimedes
To register a question, and to submit completed Archimedes topics, please email bob.phillips@doctors.org.uk first. The creation of such a topic summary follows this process:

- Selection of a clinical scenario
- Definition of the clinical question
- Search for answers
- Appraise the evidence
- Create a critically appraised topic (CAT)
- Summarise as a best evidence topic (BET)

The best evidence topic is the final accumulation of the critical appraisal. The strict format allows the casual reader to extract important information quickly and easily

Images in Paediatrics/Images in Neonatal Medicine
This is a really useful format for trainees, and those who are keen to start publishing, as well as established authors. We would welcome submissions to the above categories should take the form of a striking or clinically important image, as well as up to 250 words of text (and up to 5 references). The text should carry a brief clinical outline, and a clear clinical message or learning point. Two images can be submitted simultaneously, but this will require reducing the word count.
One tip is perhaps to compare the clinical image with Google Images, to ensure that the image is not replicating a well-known appearance. Please ensure that for all

Image submissions, you also upload a scanned patient consent form as a supplemental file. If an image is good but describing a well-known appearance: consider the criteria for submitting an Epilogue instead. The image quality should be 300x300dpi

Rapid responses to articles published

Letters in response to articles published in the Archives of Disease in Childhood are welcome and should be submitted electronically via the journal's website and NOT to Scholar One. Contributors should go to the abstract or full text of the article in question. At the top right corner of each article is a "contents box". Click on the "eLetters: Submit a response to this article" link.

Letters relating to or responding to previously published items in the journal will be shown to those authors, where appropriate.

Word count: up to 300 words

Abstract: not required

Tables/Illustrations: up to 2 (but must be essential)

References: up to 5

Editorials

These are commentaries commissioned by the editors to provide background and context for published articles.

Word count: up to 1200 words

Abstract: not required

Tables/Illustrations: up to 2

References: up to 5

Leading Articles/Reviews

These are generally commissioned. Leading articles and reviews can be discussed with either the Editor in Chief or Commissioning Editor. Editors will make the final decision regarding whether an article is classified as a leading article or review. In general reviews focus on clinical issues, whereas leading articles reflect on issues that are broader in scope than a specific clinical entity. Reviews should be no longer that 2500-3000 words (exclusive of titles, tables, figures, and references), and the word count for leading articles is at the discretion of the editor but generally 1500 – 2500

For Leading Articles the title should have no more than 10 words. No abstract is required.

For Reviews an abstract is required and should be a brief summary of the article.

Word count: 2500 – 3000 (review) and 1500-2500 (leading article)

Figures/tables: are encouraged

References: 30-40 should suffice

E&P: Self-assessment questions: Epilogue

The merit of this section is in using high-quality image(s) to remind the readers about the important features of a common clinical problem and using MCQs to produce useful learning points and take-home messages. This is also a useful format for trainees as well as established authors.

We invite readers to submit cases accompanied by questions. The text should be no more than 600 words, and might be accompanied by one or two figures, preferably clinical images, though good-quality radiology figures will be considered, and 4 or 5 MCQs. Radiology images should be of a standard that paediatricians would be able to identify the important feature and should be 300×300 dpi. Real-life cases must have parent/patient consent and be anonymised. Answers should be given, with a punchy learning point: 1 sentence each. Submissions will be peer-reviewed before publication. Authors will be credited in the journal.

If you want to know more please contact us

via info.adc@bmj.com or mpt195@hotmail.com, or to submit a question

to http://mc.manuscriptcentral.com/adc and submit under the ‘Epilogue’ category.

Word count: 600 words

Tables/Illustrations: 1-2

E&P: Equipment QI Reports

The aim of these reports is to showcase good practice in paediatric QI and to share experiences and learning. We are particularly keen to highlight both successes and failures, as it is often from the failures that we learn the most. The emphasis may be on small achievable projects led by frontline staff, not just large scale change.

Intended audience

Reports are intended for anyone interested in improving child health. We particularly hope this will inspire frontline clinicians to undertake their own QI projects. The focus is on learning and understanding the process of QI.

Style of the paper

The papers should be brief, to the point and informative, and they should be limited to one side of paper in the journal (700 words max). Our hope is that the paper would provide enough information to allow the QI work to be spread and others to make use of it.

Article structure

Please use the following headings (in capitals) and address the points within each:

- SUMMARY: Summarise your project and the clinical setting (one sentence) e.g. Implementation of a PEWs chart in a rural district general paediatric inpatient ward.
- THE PROBLEM: Why did you choose this project, what was the quality/safety issue? How did you identify the problem?
- AIMS: What were the aims of your project? Be as specific and as SMART as possible.
- MAKING A CASE FOR CHANGE: How did you communicate the need for change? Who did you need to involve in your project and how did you do this?
- YOUR IMPROVEMENTS: Outline the changes and how you implemented them, including the QI tools/techniques used e.g. PDSA cycles. How do you know the changes you made resulted in improvement? What were the outcomes of your project and how will you ensure that they are sustained?
- LEARNING AND NEXT STEPS: What would you do differently next time and what were the secrets to success (where did you find support)? What are your next steps in this project- where next?

Equipped commissioning guide

The Equipped series of articles aims to introduce readers to core Quality Improvement concepts. Using Child Health examples, change theories, improvement models and relevant resources can be demonstrated and shared. There is a strong emphasis on practical suggestions to enable readers to embark upon their own projects.

Intended audience

All child health professionals looking to undertake quality improvement work and looking for an introduction to core QI themes with examples.

Good examples are:

Patient involvement in quality improvement: is it time we let children, young people and families take the lead?

Patient involvement in quality improvement: is it time we let children, young people and families take the lead?

Robertson S, et al. Arch Dis Child Educ Pract Ed 2014;99:23–27.

Using Data to Improve Care Cheung CRLH, et al. Arch Dis Child Educ Pract Ed 2013; 98:224–229.

These are good because:

- They use specific examples to highlight a QI theory or model
- The underlying theory is clearly explained in a practical way
- They are focused on supporting readers to undertake similar work
- They use illustrations and text boxes for clarity

Specific Instructions:

Please feel free to include other authors provided their contribution is significant and adds value. Please include at least two, and preferably more, boxes, table and figures, and make use of full colour. Colour charges are not applicable in E&P. A common pitfall is to write a textbook chapter. Clues that you are doing this will include an overlong article, getting stuck in detail that only very expert readers need to appreciate, and the need for very many references. If you're falling into this trap, and want help, then your commissioning editor should be able to assist you. Many authors find this advice helpful. Your article will need to be submitted through the ScholarOne system. If you have been commissioned, please follow the instructions. Please note that as a peer reviewed journal, your article will undergo peer review. This allows us to ensure we are publishing high quality work, and our peer reviewers almost invariably help to improve papers.

Word count: maximum 3000 words excluding references, boxes, tables and diagrams. Please take a look at this paper which changed the world in around 650 words

Figures/tables: are encouraged

References: 30-40

Supplements

The BMJ Publishing Group journals are willing to consider publishing supplements to regular issues. Supplement proposals may be made at the request of:

- The journal editor, an editorial board member or a learned society may wish to organise a meeting, sponsorship may be sought and the proceedings published as a supplement.
- The journal editor, editorial board member or learned society may wish to commission a supplement on a particular theme or topic. Again, sponsorship may be sought.
- The BMJPG itself may have proposals for supplements where sponsorship may be necessary.
- A sponsoring organisation, often a pharmaceutical company or a charitable foundation, that wishes to arrange a meeting, the proceedings of which will be published as a supplement.

In all cases, it is vital that the journal's integrity, independence and academic reputation is not compromised in any way.

For further information on criteria that must be fulfilled, download the supplements guidelines.

When contacting us regarding a potential supplement, please include as much of the information below as possible.

- Journal in which you would like the supplement published
- Title of supplement and/or meeting on which it is based
- Date of meeting on which it is based
- Proposed table of contents with provisional article titles and proposed authors
- An indication of whether authors have agreed to participate
- Sponsor information including any relevant deadlines
- An indication of the expected length of each paper Guest Editor proposals if appropriate

**2.2 Detailed norms**

Title page

The title page must contain the following information:

- Title of the article.
- Full name, postal address, e-mail and telephone number of the corresponding author.
- Full name, department, institution, city and country of all co-authors.

- Word count, excluding title page, abstract, references, figures and tables.

Keywords

Authors can usually opt to (or are required to) choose keywords relevant to the content of the manuscript during the submission process. This assists in the identification of the most suitable reviewers for the manuscript. The selected keywords should also be included in the abstract itself.

Manuscript format

The manuscript must be submitted as a Word document (*BMJ Case Reports* and *Veterinary Record Case Reports* request that authors submit using a template which should also be in Word format). PDF is not accepted.

The manuscript should be presented in the following order:

- Title page.
- Abstract, or a summary for case reports (Note: references should not be included in abstracts or summaries).
- Main text separated under appropriate headings and subheadings using the following hierarchy: BOLD CAPS, bold lower case, Plain text, Italics.
- Tables should be in Word format and placed in the main text where the table is first cited. Tables should also be cited in numerical order.
- Acknowledgments, Competing Interests, Funding and all other required statements.
- References. All references should be cited in the main text in numerical order.

Figures must be uploaded as separate files (view further details under the Figures/illustrations section). All figures must be cited within the main text in numerical order and legends should be provided at the end of the manuscript.

Online Supplementary materials should be uploaded using the File Designation “Supplementary File” on the submission site and cited in the main text.

Please remove any hidden text headers or footers from your file before submission.

Style

Acronyms and abbreviations should be used sparingly and fully explained when first used. Abbreviations and symbols must be standard. SI units should be used throughout, except for blood pressure values which should be reported in mm Hg.

Whenever possible, drugs should be given their approved generic name. Where a proprietary (brand) name is used, it should begin with a capital letter.

Figures/illustrations

Images must be uploaded as separate files. All images must be cited within the main text in numerical order and legends must be provided (ideally at the end of the manuscript).

Colour images and charges

For certain journals, authors of unsolicited manuscripts that wish to publish colour figures in print will be charged a fee to cover the cost of printing. Refer to the specific journal's instructions for authors for more information.

Alternatively, authors are encouraged to supply colour illustrations for online publication and black and white versions for print publication. Colour publication online is offered at no charge, but the figure legend must not refer to the use of colours.

File types

Figures should be submitted in TIFF or EPS format. JPEG files are acceptable in some cases. A minimum resolution of 300 dpi is required, except for line art which should be 1200 dpi. Histograms should be presented in a simple, two-dimensional format, with no background grid.

For figures consisting of multiple images/parts, please ensure these are submitted as a single composite file for processing. We are unable to accept figures that are submitted as multiple files.

During submission, ensure that the figure files are labelled with the correct File Designation of "Mono Image" for black and white figures and "Colour Image" for colour figures.

Figures are checked using automated quality control and if they are below the minimum standard you will be alerted and asked to resupply them.

Please ensure that any specific patient/hospital details are removed or blacked out (e.g. X-rays, MRI scans, etc). Figures that use a black bar to obscure a patient's identity are NOT accepted.

Tables

Tables should be in Word format and placed in the main text where the table is first cited. Tables must be cited in the main text in numerical order. Please note that tables embedded as Excel files within the manuscript are NOT accepted. Tables in Excel should be copied and pasted into the manuscript Word file.

Tables should be self-explanatory and the data they contain must not be duplicated in the text or figures. Any tables submitted that are longer/larger than 2 pages will be published as online only supplementary material.

Multimedia files

You may submit multimedia files to enhance your article. Video files are preferred in .WMF or .AVI formats, but can also be supplied as .FLV, .Mov, and .MP4. When submitting, please ensure you upload them using the File Designation "Supplementary File – Video".

Authors are responsible for the accuracy of cited references and these should be checked before the manuscript is submitted.

Citing in the text

References must be numbered sequentially as they appear in the text. References cited in figures or tables (or in their legends and footnotes) should appear at the end of the reference list to avoid re-numbering if tables and figures are moved around at peer review/proof stage. Reference numbers in the text should be inserted immediately after punctuation (with no word spacing)—for example,[6] not [6].

Where more than one reference is cited, these should be separated by a comma, for example,[1, 4, 39]. For sequences of consecutive numbers, give the first and last number of the sequence separated by a hyphen, for example,[22-25]. References provided in this format are translated during the production process to superscript type, and act as hyperlinks from the text to the quoted references in electronic forms of the article.

Please note that if references are not cited in order the manuscript may be returned for amendment before it is passed on to the Editor for review.

Preparing the reference list

References must be numbered consecutively in the order in which they are mentioned in the text.

Only papers published or in press should be included in the reference list. Personal communications or unpublished data must be cited in parentheses in the text with

the name(s) of the source(s) and the year. Authors should request permission from the source to cite unpublished data.

Journals from BMJ use a slightly modified version of Vancouver referencing style (see example below). Note that The BMJ uses a different style.

List the names and initials of all authors if there are 3 or fewer; otherwise list the first 3 and add ‘et al.’ (The exception is the Journal of Medical Genetics, which lists all authors). Use one space only between words up to the year and then no spaces. The journal title should be in italic and abbreviated according to the style of Medline. If the journal is not listed in Medline then it should be written out in full.

Example references

Journal article

13 Koziol-Mclain J, Brand D, Morgan D, et al. Measuring injury risk factors: question reliability in a statewide sample. *Inj Prev* 2000;6:148–50.

Chapter in book

14 Nagin D. General deterrence: a review of the empirical evidence. In: Blumstein A, Cohen J, Nagin D, eds. Deterrence and Incapacitation: Estimating the Effects of Criminal Sanctions on Crime Rates. Washington, DC: National Academy of Sciences 1978:95–139.

Book

15 Howland J. Preventing Automobile Injury: New Findings From Evaluative Research. Dover, MA: Auburn House Publishing Company 1988:163–96.

Abstract/supplement

16 Roxburgh J, Cooke RA, Deverall P, et al. Haemodynamic function of the carbomedics bileaflet prosthesis [abstract]. *Br Heart J* 1995;73(Suppl 2):P37.

Electronic citations

Websites are referenced with their URL and access date, and as much other information as is available. Access date is important as websites can be updated and URLs change. The “date accessed” can be later than the acceptance date of the paper, and it can be just the month accessed.

Electronic journal articles

Morse SS. Factors in the emergency of infectious diseases. *Emerg Infect Dis* 1995 Jan-Mar;1(1). www.cdc.gov/nciod/EID/vol1no1/morse.htm (accessed 5 Jun 1998).

Electronic letters

Bloggs J. Title of letter. *Journal name* Online [eLetter] Date of publication. url eg: Krishnamoorthy KM, Dash PK. Novel approach to transseptal puncture. *Heart* Online [eLetter] 18 September 2001. http://heart.bmj.com/cgi/eletters/86/5/e11#EL1

Legal material

Toxic substances Contro Act: Hearing on S776 Before the Subcommittee of the Environment of the Senate Comm. on Commerce, 94th Congress 1st September (1975).

Washington v Glucksberg 521 US 702 (1997)

Law references

The two main series of law reports, Weekly Law Reports (WLR) and All England Law Reports (All ER) have three volumes a year.

For example:

Robertson v Post Office [1974] 1 WLR 1176

Ashcroft v Mersey Regional Health Authority [1983] 2 All ER 245

R v Clarence [1868] 22 QBD 23

Wimpey Construction UK Ltd v Poole (1984) Times, 3 May

There are good historical precedents for the use of square and round brackets. Since 1891, round ones have referred to the date of the report, square ones to the date of publication of the report. Apart from not italicising the name of the case, we use the lawyers' style; be careful with punctuation. Here are some more examples:

Caparo Industries plc v Dickman and others [1990] 1 All ER 568-608.

R v Clarence [1888] 22 QBD 23.

Finlayson v HMAdv 1978 SLT (Notes) 60

Block v Martin (1951) 4 DLR 121

Official Journal of the European Communities: at the top of the page it gives the No, vol, and page and, at the other side of the header, the date.
The abbreviation for the title is given in parentheses under the title. Jiggle these elements around to get, eg: Council Directive of 14 June 1989. Offical Journal of the European Communities No L 1989 June 28:181/44-6. (89/831/EEC.

Digital Object Identifier (DOI)

A DOI is a unique string created to identify a piece of intellectual property in an online environment and is particularly useful for articles that are published online before appearing in print (and therefore have not yet been assigned the traditional volume, issue and page number references). The DOI is a permanent identifier of all

versions of an article, whether raw manuscript or edited proof, online or in print. Thus the DOI should ideally be included in the citation even if you want to cite a print version of an article.

How to cite articles with a DOI before they have appeared in print

1. Alwick K, Vronken M, de Mos T, et al. Cardiac risk factors: prospective cohort study. *Ann Rheum Dis*Published Online First: 5 February 2004. doi:10.1136/ard.2003.001234

How to cite articles with a DOI once they have appeared in print

1. Vole P, Smith H, Brown N, et al. Treatments for malaria: randomised controlled trial. *Ann Rheum Dis*2003;327:765–8 doi:10.1136/ard.2003.001234 [published Online First: 5 February 2002].

PLEASE NOTE: RESPONSIBILITY FOR THE ACCURACY AND COMPLETENESS OF REFERENCES RESTS ENTIRELY WITH THE AUTHOR.

# 3 ARTIGO ORIGINAL

**Use of histamine-2 receptor antagonists is associated with infection in newborns hospitalized, but not necrotizing enterocolitis and mortality: a systematic review and meta-analysis**

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**Funding:** This study had no financial support.

**Competing interests:** The authors declare that they have no competing interests.

**Abstract**

***Background:*** Histamine-2 receptor antagonists ($H_2RA$) have been commonly prescribed "off label" in neonate hospitalized in neonatal intensive care unit (NICU). Some studies showed that the use of $H_2RA$ may predispose to infections, necrotizing enterocolitis (NEC) and mortality in this population. This meta-analysis systematically examined the association between $H_2RA$ and infections, NEC and mortality in preterm infants.

***Methods:*** A systematic review was made using PubMed, Web of Science and SCOPUS databases up to April 30, 2017. Publications were identified using the search terms "histamine-2 receptor antagonists", "infection", "necrotizing enterocolitis", "mortality" and related terms. Forest plot test was used to graphically present the effect sizes and the 95% confidence interval for the six conditions/terms (infection; pneumonia; sepsis; NEC; urinary tract infection; mortality).

***Results:*** Three case–control and three cohort study were included. Meta-analysis showed a significant association between infection and $H_2RA$ (RR of 2.13, 95%CI: 1.20 –3.78). Specific analysis found higher incidence of sepsis (RR 2.39; 95%CI: 1.09-5.23; $I^2$ = 91%), pneumonia (RR 2.70; 95%CI: 1.41-5.19; $I^2$ = 0%) and urinary tract infection (RR 8.32; 95%CI: 2.32-29.91; $I^2$ = 91%) in $H_2RA$ neonates.

***Conclusions:*** Exposure to $H_2RA$ is associated with increased risk of infections in preterm infants.

## Introduction

Histamine-2 receptor antagonists ($H_2RA$) have been commonly prescribed *off-label* to newborns admitted to neonatal intensive care units (NICU), because of their safety and efficacy in older populations[1]. In NICU, the most common indications for the administration of $H_2RA$ are prophylaxis or therapy of stress ulcers and gastroesophageal reflux disease, but their safety and efficacy in preterm infants is still debated[2]. Some studies showed that the use of $H_2RA$ may predispose to infections[3,4,5,6,7,8], necrotizing enterocolitis (NEC)[6,9,10,11] and is associated with mortality[6], however there is no systematized evidence to support this association. Thus, we conducted a systematic review and meta-analysis to investigate if the use of $H_2RA$ by preterm newborns is associated or not with infection, NEC and mortality.

## Methods

### *Search strategy and selection criteria*

We performed a systematic review using PubMed, Web of Science and SCOPUS databases to identify studies published in Portuguese, Spanish and English up to April 30, 2017. Publications were identified using the search terms “histamine-2 receptor antagonists”, “infection”, “necrotizing enterocolitis”, “mortality” and related terms. Two independent reviewers (MSF and RNSS) screened titles and abstracts for relevance and adequacy. Disagreements were resolved by VSS and RQG. Relevant studies were read in full-text and selected according to eligibility criteria. The reference lists of all eligible studies and reviews were also manually scanned to identify additional studies for inclusion. We included observational studies that have been conducted with hospitalized neonates exposed or not to a histamine-2 receptor antagonist. Primary outcomes included infection, NEC, and mortality. Secondary outcomes included pneumonia, sepsis and urinary tract infection (UTI). We excluded studies conducted with children over 28 days of age, studies reporting data from a

community population and those including neonates having previous infections, malformations, genetic syndromes, born from mothers with HIV, rubella, toxoplasmosis, cytomegalovirus, hepatitis B and C. Studies not containing original material were also excluded.

***Data extraction and bias assessment***

Pre-defined tables were used for data extraction. The information extracted included author, publication year, country, study design, sample size, number of neonates having infection and/or NEC and who died according to the exposition or not to $H_2$RA. Not all studies reported the absolute number for each outcome and percentages were used to calculate them. The quality of studies and the risk of bias were assessed by two independent reviewers using the Newcastle-Ottawa Scale (NOS).

***Statistical analysis***

We calculated the pooled relative risk (RR) for infection, NEC, and mortality in hospitalized children using $H_2$RA. A forest plot was used to graphically present the effect sizes and the 95% confidence interval (95%CI). Each study was represented by a square in the plot that was proportional to the study's weight in the meta-analysis. A 2-tailed $p < 0.05$ was used to determine significance. Statistical heterogeneity was assessed using the Cochran Q test[12] and quantified by the $I^2$ index[13]. A subgroup analysis was performed according to the study design (cohort or case-control study). Pooled RR was also calculated for secondary outcomes.

"Leave-one-out" sensitivity analysis was conducted by omitting one study at a time and examining the influence of each individual study on the pooled effect size[14]. Analysis were performed using R statistical programming language version 2.10.13.

**Results**

The search identified 1,144 records. After screening titles and abstracts, 35 full-text articles were assessed for eligibility and six were included (Figure 1). Table 1 summarize the main characteristics of each study. Three of six articles included were cohort studies[6,7,8] and three

were case-control studies[5,15,16]. Most studies[5,6,7,15,16] included very-low birth weight as their population and only one study[8] was less specific and considered the whole preterm population (gestational age < 37 weeks). Study size ranged from 76 to 569 neonates. All the articles analyzed infection as an outcome and three of them[6,8,15] also included NEC and mortality rates.

The six observational studies included 2,143 subjects. 290 (56.1%) of 515 neonates who received $H_2RA$ treatment had infection whereas only 366 (22.5%) of the 1,628 who were not exposed to $H_2RA$ treatment had infection, resulting in a pooled RR of 2.13 (95%CI: 1.20 – 3.78) (Figure 2). There was substantial between-study heterogeneity ($I^2$: 92.1%) and the sub-group meta-analysis showed that cohort studies influenced the pooled RR. There was substantial between-study heterogeneity ($I^2$: 92.1%).

Some studies presented data for types of infection and we explored their results (Figure 3 A, B, C). Four studies[5,6,8,15] involving 1,503 neonates had data for sepsis and the pooled RR was 2.39 (95%CI: 1.09-5.23; $I^2$ = 91%). Three studies[6,8,15] reported both pneumonia and urinary tract infection data, and the pooled RR was 2.70 (95%CI: 1.41-5.19; $I^2$ = 0%) and 8.32 (95%CI: 2.32-29.91; $I^2$ = 91%), respectively.

Figures 4 and 5 show that the use of $H_2RA$ was not associated with the risk for NEC and mortality, but the mortality outcome was influenced by the cohort studies and showed a RR of 4.24 (95% CI 2.40 – 7.46) in these studies.

**Discussion**

The association between $H_2RA$ and infection, NEC or mortality could be evaluated using 6 papers in two different study models (3 cohorts and 3 case-control). Overall meta-analysis indicate that $H_2RA$ is associated to the increasing of infection rates, including pneumonia and sepsis. Otherwise, they did not show relation between this drug and NEC or mortality.

Nosocomial infections are the major cause of death in hospitalized neonates. The main known risks are prematurity, low birth weight, mechanical ventilation, central catheter peripherally inserted and parenteral nutrition[4,5,7]. The use of gastric acid secretion inhibitors as $H_2$RA suppresses one of the major infants immune defense and predisposes to pathogens gastric colonization[17]. Many studies suggested association between the treatment with $H_2$RA and infection, including pneumonia[1,18], late sepsis and UTI[4,5,6,7,8,10], and some of them[1,6,7,8,9,17] included these drugs as an important risk factor for NEC as well. However, Singh et al. (2016)[15] and Santana et al. (2017)[8] findings did not identify association between ranitidine and NEC.

Terrin et al. (2012)[6] studied 274 VLBW newborns and concluded that the use of ranitidine raises 7 times the risk of NEC in comparison to the control group. This prospective study finding was not related to dosage or duration of ranitidine therapy. Infection, as sepsis, urinary tract infection or pneumonia and death were also more frequent in the group receiving ranitidine. Afjeh et al. (2012)[7] had 564 VLBW infants enrolled in their retrospective study. Among them, 52,7% of the neonates receiving ranitidine had nosocomial infection comparing to 17,4% who did not receive. It did not report NEC or mortality. Santana et al. (2017)[8] evaluated 300 preterm neonates and the ones who received ranitidine were more likely to have nosocomial infection, confirmed sepsis and pneumonia. This study also identified that the treated group had 4 times more risk of death. However, NEC was not associated with ranitidine. However, these studies did not report the complete feeding data, important and known factor to NEC and the causes of death were not clear, being precipitated to directly associate them with $H_2$RA use.

The studies included in this review had an important heterogeneity ($I^2$: 92.1%) in their samples. It is important to emphasize that the cohort studies are more relevant in their accuracy. The mean dosage of ranitidine and the duration of treatment was supposed to be

evaluated among these studies, however this data was not available in all of them. The papers which had the mean dosage registered range from 1,1[9] to 6,9[16] mg/kg/per day, a relevant interval that could interfere in the outcomes.

Singh et al. (2016)[15] reported no association between H2 blockers and infection, NEC or mortality. This conflicting outcome can be explained by the difference in dosage and duration of H2 blocker treatment from other papers[6,9] or specially because the average time of treatment beginning was 37-72 days after birth. This could have allowed time for maturation of immune system, making these neonates less susceptible to infection or NEC.

**Conclusion**

The use of $H_2RA$ is associated with infection in neonates hospitalized, but not with necrotizing enterocolitis or death. The results were mainly affected by the cohort studies, what emphasizes the needing of more research following this kind of study design. Dosage and duration of $H_2RA$ should be more carefully observed and feeding protocol can be an important factor to NEC outcome and cause of bias.

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**List of tables and figures**

**Table 1. Main characteristics of the analyzed studies**

| Study | Country | Study design | Population | Subject characteristics | Outcome |
|---|---|---|---|---|---|
| Afjeh et al. (2012)[8] | Iran | Cohort | Very Low Birth Weight | Birth weight: 750-1500g<br>GA (median): 28 weeks | Infection |
| Santana et al. (2017)[9] | Brazil | Cohort | Pre-term | Birth weight (median): 1442g;<br>GA (median): 32 weeks | Infection, NEC and mortality |
| Terrin et al. (2012)[6] | Italian | Cohort | Very Low Birth Weight | Birth weight: 401-1500g<br>GA: 24-32 weeks | Infection, NEC and mortality |
| Gupta et al. (2013)[16] | USA | Case-control | Very Low Birth Weight | Birth weight (median): 1000g<br>GA (median): 27,5 weeks | Infection |
| Singh et al. (2016)[15] | Australia | Case-control | Very Low Birth Weight | Birth weight: < 1500g | Infection, NEC and mortality |
| Bianconi et al. (2007)[5] | USA | Case-control | Very Low Birth Weight | > 7 days in NICU | Infection |

**GA:** Gestational Age; NEC: Necrotizing Enterocolitis

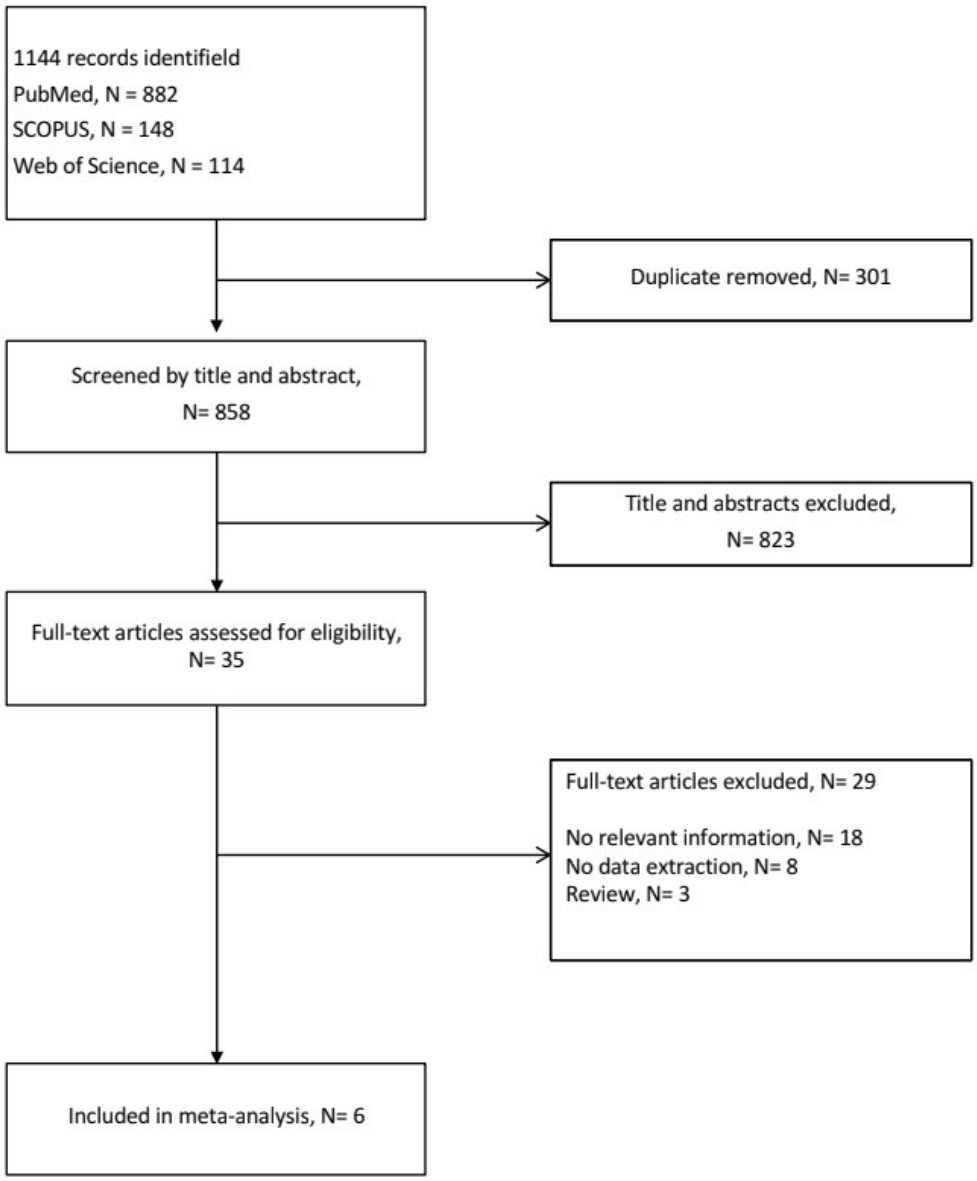


**Figure 1. Flowchart of studies for inclusion in the meta-analysis**

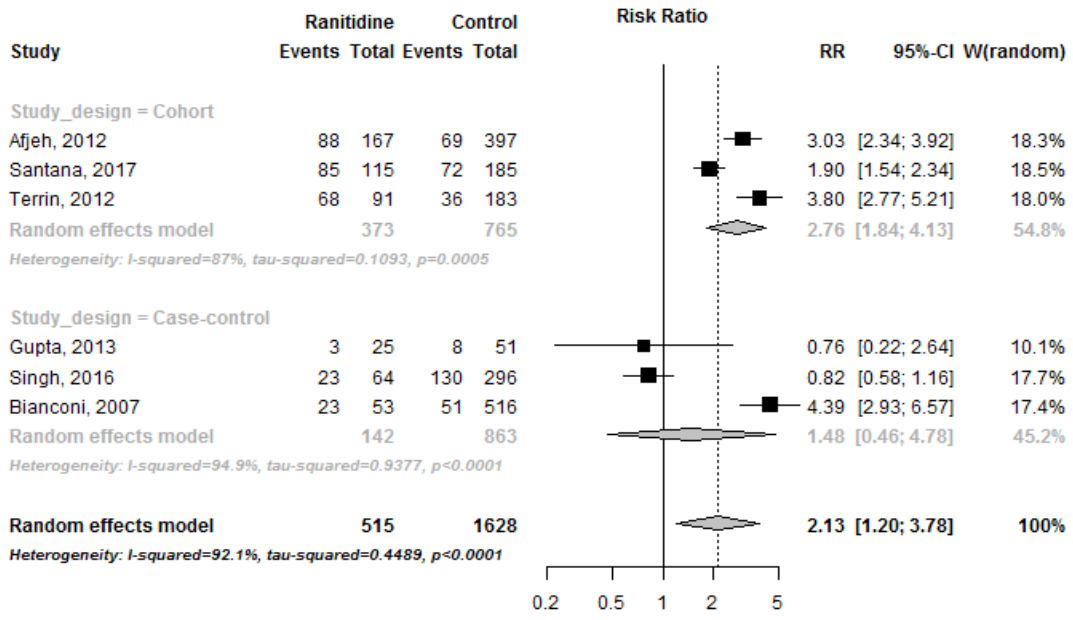


**Figure 2. Results for infection outcome**

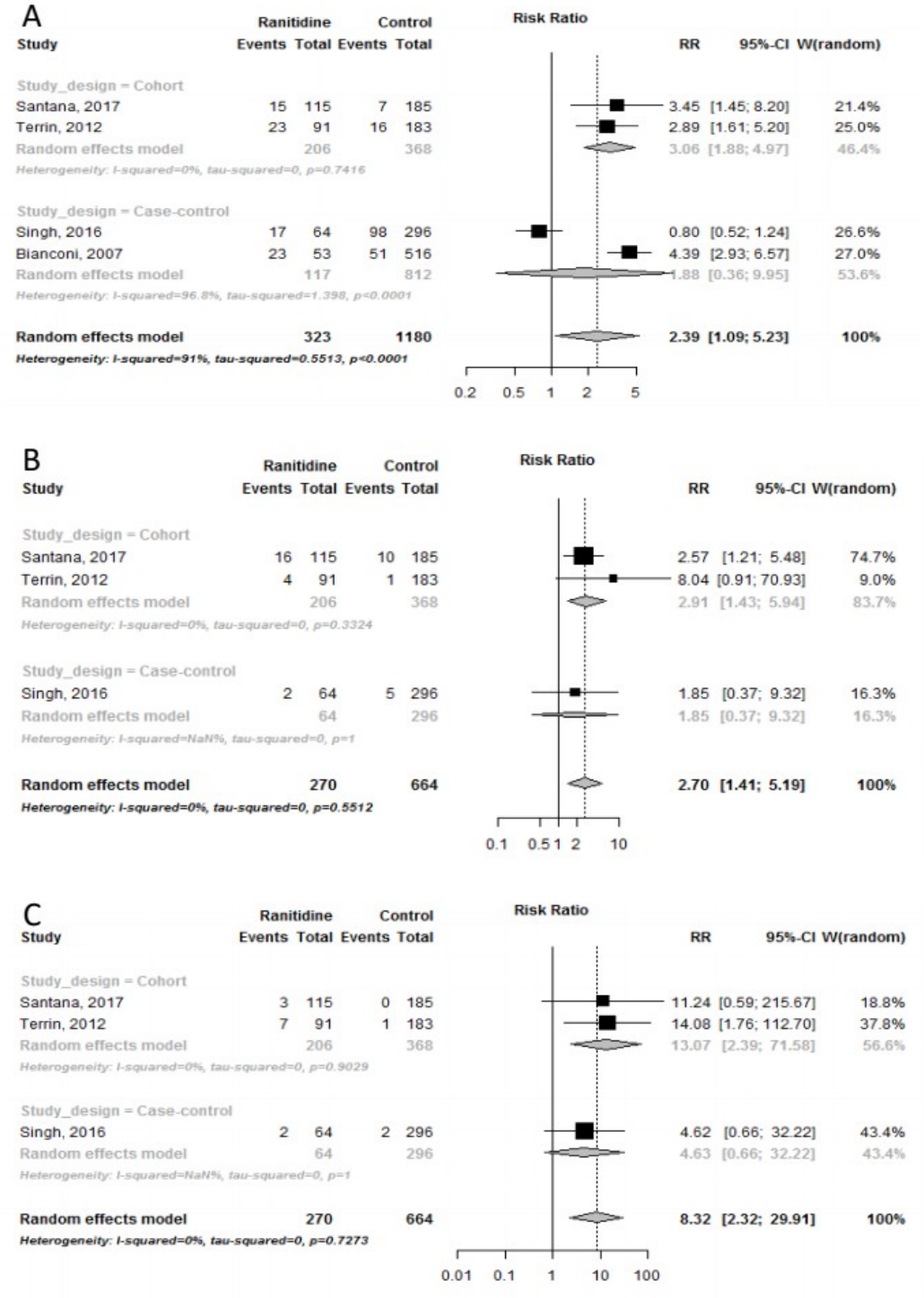


**Figure 3. A) Results of sepsis outcome B) Results of pneumonia outcome C) Results of urinary tract infection outcome**

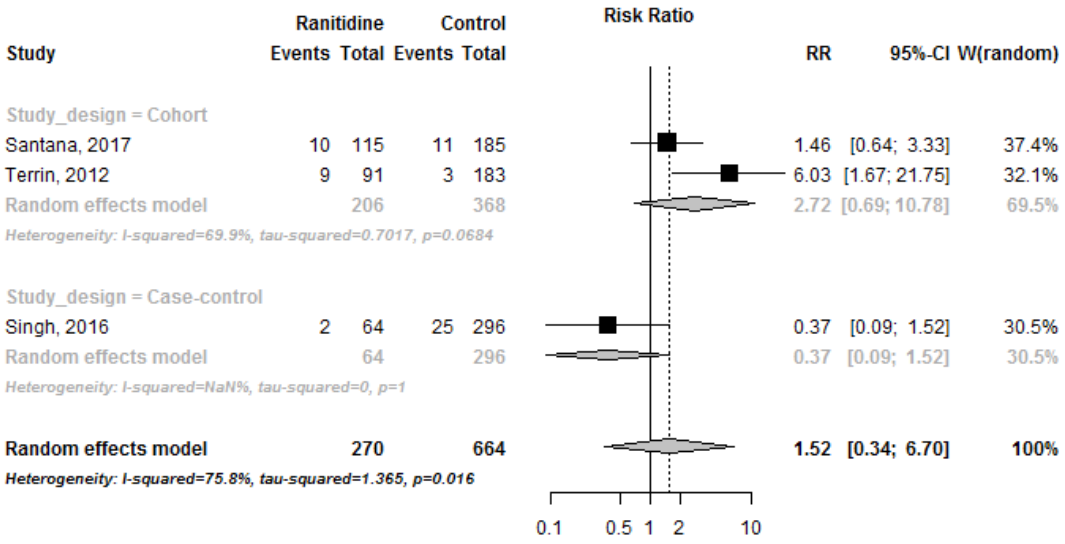


**Figure 4. Results of Necrotizing Enterocolitis outcome**

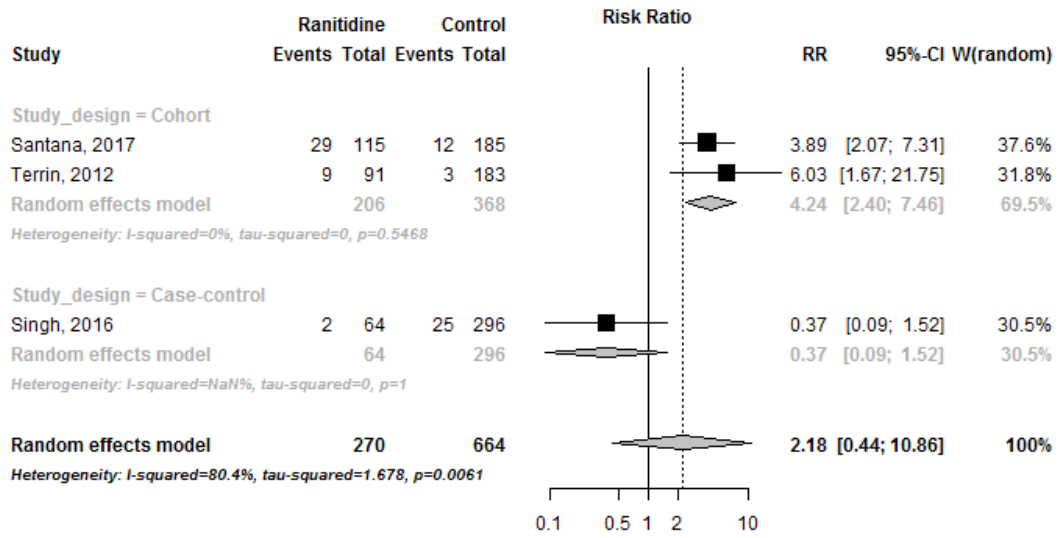


**Figure 5. Results of mortality outcome**