ORIGINAL RESEARCH

Rhizobium radiobacter – related infection in neonates: A systematic review

[1]Niranjan Kamble, [2]Darshan Rajatadri Rangaswamy, [3]Kiran Kavatagi

[1,2]Assistant Professor, Department of Pediatrics, Subbaiah Institute of Medical Sciences, Shimoga, Karnataka, India
[3]Associate Professor, Department of Microbiology, Subbaiah Institute of Medical Sciences, Shimoga, Karnataka, India

Corresponding author
Darshan Rajatadri Rangaswamy
Assistant Professor, Department of Pediatrics, Subbaiah Institute of Medical Sciences, Shimoga, Karnataka 577222, India
Email-rajatadri93@gmail.com

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ABSTRACT

Background: Rhizobium radiobacter is a gram-negative bacillus, gaining attention as a human pathogen. In the past, these infections were primarily observed in immunocompromised individuals. However, recently, cases have been reported in healthy individuals, including newborns. The main objective of this study is to conduct a comprehensive review of *R. radiobacter* infections in neonates, including their clinical features, diagnostic methods, treatment options, and outcomes. **Methods:**A systematic search of PubMed, Cochrane Library, DOAJ, and Google Scholar identified relevant studies reporting *R. radiobacter* infections in neonates. Inclusion criteria comprised full-text publications reporting neonatal infections, human subjects, and English language. Data extraction included patient demographics, diagnoses, treatments, and outcomes. Statistical analysis employed SPSS version 24. **Results:**Among 55 initially identified publications, eight met inclusion criteria after screening. Predominantly, infections presented as bacteremia and neonatal sepsis. The presentation was that of late-onset sepsis in the majority of cases. Most cases were sensitive to Carbapenems (75%), Aminoglycosides (62.5%) and Fluoroquinolones (50%) with variable sensitivity to Cephalosporins. Trimethoprim-sulfamethoxazole resistance was predominant (37.5%). Most neonates recovered after responding to antibiotics, but two deaths occurred, one unrelated to *R. radiobacter.* **Conclusion:** Rhizobium radiobacter once considered a contaminant, is gaining recognition, affecting both immunocompromised and healthy neonates. While predominantly associated with bacteremia, this review revealed varied susceptibility profiles with potential resistance to colistin. Recognition of its clinical impact on neonates is vital for timely and effective treatment. This study highlights the importance of early identifying and managing*R. radiobacter* infections in neonates.

INTRODUCTION

Rhizobium radiobacter is a gram-negative, non-sporing, motile bacillus, an emerging human pathogen.[1,2] Though most infections earlier were attributed to an immunocompromised state or in those with indwelling devices, there is increasing evidence of it affecting otherwise healthy individuals.[3–6]Little is known about its effect on neonates.The purpose of this study was to conduct a systematic review of *R. radiobacter* infections in the neonatal population that have been established by bacteriology. A secondary goal was characterising the clinical traits, diagnostics, treatment approaches, and outcomes of neonates with *R. radiobacter* infection.

MATERIALS AND METHODS

Pubmed (https://www.ncbi.nlm.nih.gov/pubmed/), Cochrane Library(http://www.cochranelibrary.com/) databases,Directory of Open Access Journals (DOAJ), Science direct and Google Scholar (till January 16, 2024) were systematically searched for studies reporting infection caused by *R. radiobacter*. We used the search phrases "*Rhizobium radiobacter*" AND Neonates NOT Adultsto find clinical studies to review. The titles and abstracts of the retrieved publications were reviewed for eligibility. The following inclusion criteria were used to select studies for further analysis: (1) full-text publication/abstract reporting at least one *R. radiobacter-related* infection in neonates; (2) enrolling human subjects; and (3) in English. Conference reports, remarks, and findings from studies using animals or cell lines were removed. Citations selected were included in the final analysis if these following data were available: documentation of infection in neonates and confirmation of *R. radiobacter* detection by cultures.All data were

independently abstracted in triplicate by three investigators (NK,DRR,KK) according to the inclusion criteria. The first author's last name, the publication year, the age of the reported patients, gestational age at birth, their diagnosis, birth weight, underlying condition, the complications encountered, the method of bacterial isolation, the bacterial antimicrobial susceptibility and resistance profiles, the initiated treatment, as well as the outcomes, were all information that was retrieved from each publication. SPSS1 version 24 was used to descriptively analyse the extracted data (IBM, Armonk, NY, USA).

RESULTS

Our literature review yielded eight publications from Pubmed, none from Cochrane Library, one from DOAJ, 44 from Science Direct and eight from Google Scholar, of which 6 were duplicates and hence removed. Out of 55, we excluded 46, as 4 were non-human studies, 41 were unrelated, and one was in the non-English language. Out of the remaining nine studies, one had pseudobacteremia and was removed. The remaining eight publications were further evaluated. A flow diagram summarising the literature research approach is shown in Flowchart 1. A triplicate screening was done, and all 8 met our inclusion criteria and were analysed for our systematic review. We were able to find a total of 8 cases of *R. radiobacter*-related infections in neonates. The clinical details of these 8 cases are summarised in Tables 1 and 2.Eight papers were reporting *R. radiobacter* infection in neonates enrolled, five patients of which were preterm & 3 were of term gestation. Bacteraemia was the predominant diagnosis and was seen in 5 neonates & 2 were classified as neonatal sepsis, and one was diagnosed as Central line associated blood stream infection (CLABSI). All patients were treated with antibiotics, and most recovered—one developed complications unrelated to infection. There were two deaths, one related to non-*R. radiobacter*-related preterm complications and the other due to sepsis.Two patients were noted to have underlying birth anomalies. The majority of the babies presented with symptoms of late-onset sepsis, with fever, lethargy and refusal to feed being common. Underlying risk factors like premature rupture of membranes (PROM) were noted in 2, and 2 had other bacterial sepsis and one received steroid. Only two cases had central venous access. The average blood culture flagging time was 24-48hrs with two studies yielding reports at 72 hrs. The common method used to isolate the bacteria was conventional with Vitek 2; however, three studies used BACT/ALERT 3D with Vitek2 and one with BACTEC with Vitek 2&Vitek MS method. All of the cases were sterile at CSF cultures. The isolates were sensitive to Carbapenems (75%), Aminoglycosides (62.5%), Fluoroquinolones (50%), Beta-lactam (25%) and Tetracycline (12.5%) with variable sensitivity to Cephalosporins. Resistance to Trimethoprim-sulfamethoxazole (37.5%) was predominant, followed by Beta-lactams (25%), Aminoglycosides (25%), and Fluoroquinolones (12.5%) and Colistin (12.5%).All neonates were treated with antibiotics, averaging 10-14 days. Six out of 8 babies were discharged after recovery; however, there were two mortalities, one of which was due to non-infectious complications and another due to sepsis, the direct causation of *R. radiobacter* was, however, unclear.

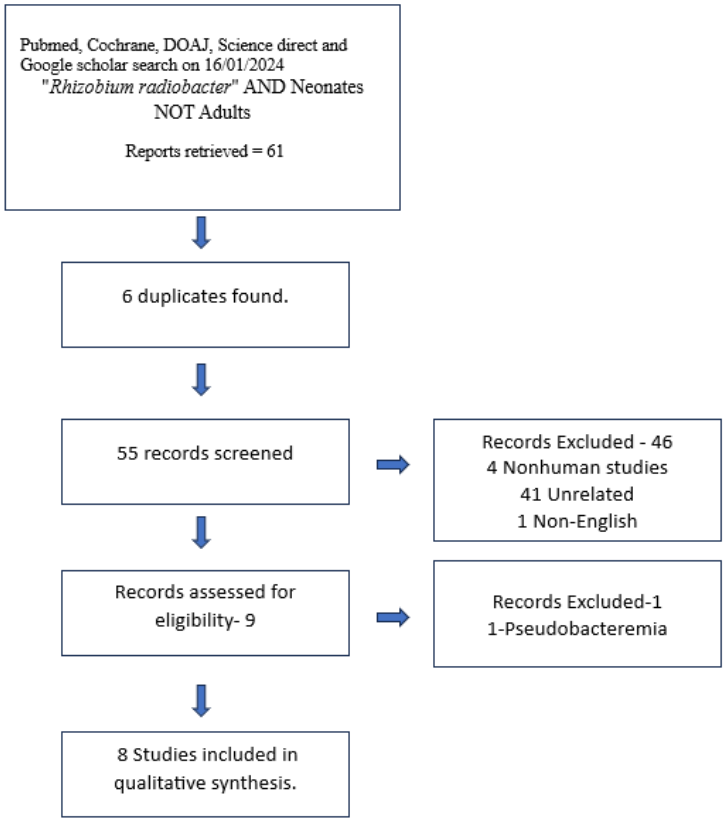
Table 1: Clinical and microbiological characteristics of R.radiobacter infections in neonates

Reference/year	Type of Study	Diagnosis	Age (days)	Gestation/ Weight	Underlying condition	Positive BC time	CL	Method of isolation & identification from blood	Susceptible	Resistant	Complication	Treatment	Outcome
Triadi et al. 2022	CR	Neonatal sepsis	1	Preterm/2.2 kg	Birth asphyxia	NS	NS	NS, Vitek 2	Levo	NS	NS	Ampi, Amika, Mero	Died - day 28
Waseemoddin et al. 2022	CR and ROL	Neonatal sepsis	46	Preterm (28 wk)/ 1.26kg	NEC, 2-course antibiotics Staph epidermis sepsis, PDA	72hrs	NO	NS	Cefepime, Genta, Amika, Mero, Imip	Tmp/Smx	None	Cefepime 10 day	Recovered Discharged 38 weeks of life
Bhansali et al. 2020	CR	CLABSI	21	Preterm (34 wk)/ NS	Jejunal obstruction, PICC for TPN	24-48hrs	YES	Bactec, Vitek	Carbapenem, Cephalosporin-Variable	Amino, Fluro	NS	Mero, colistin-14 days	Recovered Discharged – day 44
Surpam et al. 2019	CR	Bacteremia	2	Preterm/ 1.2kg	Steroid use, PROM	<24hrs	NO	NS and Vitek 2	Genta, Imip, Cipro, Levo, Tige, Mino, Tmp/Smx	Ptz, TCa, Cefo, Cesu, Amika, Colistin	None	Van and PTz changed to Genta, and Imi 10 days	Recovered Discharge-day 20
Tiwari et al. 2015	CR	Bacteremia	4	Term/ NS	PROM	<24hrs	NO	BACTALERT, VITEK 2	Gent, Amik, Cefo, Ceftr, Cefe, Cipro, Imip, Mero, Pptz, Levo, TCa,	Tmp/Smx, Azt	NS	Genta and Van changed to Genta + Imi 10 days	Recovered Discharged
Khan et al. 2013	CR	Bacteremia	115	Preterm (25wk)/ 810gm	Anomalies, NEC, Klebsiella sepsis	24-48hrs	YES	Bactec, Vitek 2 and Vitek MS	Cefo, Cefuroxime, Mero, Amika	Cephalothin, Ceftazidime	pneumothorax, PAH, BPD, NEC	Mero + Amika 21 days	Death on 143 days, due to other complications
Kaselitz et al. 2011	CR	Bacteremia	1	Term/ NS	Home delivery	24-48hrs	NO	Conventional and API	Cefe, Ptz, Azt, Mero, Genta, Tobra, Amika, Tetra, Cipro, Levo	Tmp/Smx	None	Ampi, Genta changed to Cefe 14 days	Recovered Discharge- day 14
Farina et al. 1996	CR and ROL	Bacteremia	13	Term/3720g	None	72hrs	NO	NS	NS	NS	NO	Ampi + Genta 7 days	Recovered discharged after 9 days

CR-Case Report, ROL-Review Of Literature, NS- Not Specified, WK- weeks, Gm- gram,hrs- hours, CLABSI- Central Line associated blood stream infection, PROM- Premature rupture of membranes, NEC-Necrotizing Enterocolitis, PDA- Patent Ductus Arteriosus, PICC- Peripherally Inserted Central Catheter, TPN-Total Parenteral Nutrition, BPD-Bronchopulmonary dysplasia,Azt- Aztreonam, Ampi-Ampicillin, PTz-Piperacillin Tazobactam, , TCa-Ticarcillin+ Clavulanic Acid, Tmp/Smx-Trimethoprim Sulfamethoxazole, Cefe- Cefepime, CeSu- Cefoperazone + Sulbactam, Cefo-Cefotaxime, Ceftr- Ceftriaxone, Fluro- Fluroquinolone, Levo-Levofloxacin, Cipro- Ciprofloxacin, Amino-Aminoglycoside, Tobra-Tobramycin, Genta-Gentamicin, Amika- Amikacin, Mero- Meropenem, Imip- Imipenem, , Tige-Tigecycline, Van-Vancomycin, Tetra- Tetracycline, Mino- Minocycline, PAH-Pulmonary arterial hypertension, BC- blood culture, CL-central lineNS- Not specified, CRT- Capillary Refill Time, CSF-Cerebro spinal fluid

Table 2: Clinical details related to presenting symptoms, CSF results and duration of antibiotics.

Reference & year	Clinical features	Day of life of symptom onset	CSF Culture	Duration of Antibiotics (days)
Triadi et al. 2022	Grunting, prolonged CRT, mottling, respiratory distress, abdominal distension	1	NS	NS
Waseemoddin et al. 2022	Apnea, desaturations, poor feeding lethargy	46	Sterile	10
Bhansali et al. 2020	Lethargic, apnea, paleness	21	Sterile	14
Surpam et al. 2019	Fever, lethargy, refusal to feeds and respiratory distress	2	NS	10
Tiwari et al. 2015	Fever, lethargy, refusal to feeds, tachypnea	4	NS	10
Khan et al. 2013	Fever, abdominal distension	115	Sterile	21
Kaselitz et al. 2011	Cyanosis, apnea, bradycardia	1	Sterile	14
Farina et al. 1996	Fever, agitation, refusal to feed	13	Sterile	7



Flowchart 1: PRISMA flow diagram of describing inclusion and exclusion criteria for experimental studies.

DISCUSSION

The genus *Rhizobium*, previously known as *Agrobacterium*, is a well-known plant pathogen present worldwide.These contain a large tumour-inducing plasmid, producing infection and neoplastic changes in many plant species. There are five distinct species of *Agrobacterium*: *A. radiobacter* (previously known as *A. tumefaciens* and CDC group Vd3), *A. rhizogenes* (transferred to Sphingomonas rosa), *A. vitis, A. undicola and A. rubi*.[1,2,7] Young and colleagues proposed including all Agrobacterium species under *Rhizobium*, after which they were renamed R. radiobacter, *R. rhizogenes*, *R. rubi*, *R.undicola* and *R. vitis*.[8] Later, based on their evidence on classical and molecular comparisons, Farrand and colleagues found Agrobacteria biovars 1 and 3 different from members of the Rhizobium genus.[9] They suggested retaining them in the genus Agrobacterium. The nomenclature controversy continues, but we will adopt Young et al.'s proposal and refer to it as *Rhizobium radiobacter* moving forward.[8]*R. radiobacter* is the only species known to cause human infections. *R. radiobacter* is a gram-negative bacillus, a non-spore-forming aerobic bacteria that grows readily on 5 % Blood and MacConkey agar.[7] Colonies grow optimally at 25 – 28 ^{0}C but will grow also at 35^{0}C. On blood agar, colonies are circular, convex, smooth and non-pigmented to light beige and wet and become extremely mucoid and pink on MacConkey agar with prolonged incubation (>48 hrs.). They are rapid urease producers, hydrolyse esculin slowly and are positive for phenylalanine deaminase. They are oxidase- and catalase-positive and motile with peritrichous flagella. It oxidisesglucose, xylose, lactose, mannitol, adonitol and dulcitol on Hugh-Leifsons Oxidative- Fermentative medium. *R. radiobacter* strains are universally susceptible to fluoroquinolones, cephalosporin, tetracyclines and Carbapenems and should be considered for initial therapy. Acquired resistance is common with Beta-lactam antibiotics and aminoglycosides, gentamicin being more active than tobramycin.[1,2,7]*R. radiobacter* was earlier regarded as a contaminant but has gained recognition as a human pathogen in the last four decades.[4]*R. radiobacter* infections are frequently reported in those with intravascular cathetersor immunocompromised patients, mainly in malignancy.[5,7]Contrary to this, the latest literature review reveals that it affects healthy individuals, including neonates and those without catheters.Owing to its low virulence, *R. radiobacter* is most frequently isolated from blood. However, instances of it being found in peritoneal dialysate, urine, and ascitic fluid are also noted. Most of these are community-acquired, but nosocomial transmission has been noted several times.It has been found to cause infection of various sites, such as pneumonia, urinary tract infections, peritonitis, cellulitis, wound infections, cerebral abscesses, and endocarditis, most of which in healthcare settings were device-related.[1,2]Primarily, it was attributed to diseases in adults and children, with only eight identifiable neonate cases to date in published literature.[4,5,10–15] Among these, five neonates were preterm, and three were of term gestation. The primary diagnosis in most cases was bacteremia, observed in five neonates. At the same time, two were classified as neonatal sepsis, and one was diagnosed with CLABSI. The symptoms resembled that of late-onset sepsis in the majority of cases. Though it caused infection among preterm neonates with central catheters and in those who received IV antibiotics, it is noteworthy to find it affecting healthy newborns too.[4,10,14] This is substantiated by multiple reports of *R. radiobacter* affecting healthy adults and children.[3,6] The organism was readily identifiable by conventional and automated blood culture systems with average positivity by 24-48 hours. Though *R. radiobacter* is known to be universally susceptible to fluoroquinolones, cephalosporin, tetracyclines and Carbapenems and resistant to Beta-lactam antibiotics and aminoglycosides, our review revealed exciting findings; apart from being sensitive to carbapenems and fluoroquinolones, most cases were also sensitive toaminoglycosides(62.5%), Beta-lactam (25%) and tetracycline (12.5%) with variable sensitivity to cephalosporins. The majority of the isolates showed resistance to Trimethoprim-sulfamethoxazole (37.5%).Resistance to beta-lactamsand aminoglycosides was noted in 25% of cases.One case demonstrated resistance to fluoroquinolones. It was noteworthy that one case had resistance to colistin, which is alarming.[12]In all the cases, there was no evidence of isolation of the bacillus from any other source.Five cases were noted to have risk factors for nosocomial infections, including prematurity, central catheters, steroid use, antibiotic use before infection and surgery. Only 2 cases in our review had central catheters; however, only one had CLABSI. However, it is noteworthy that even three otherwise healthy neonates also contracted the infection. No notable complication was directly related to *R. radiobacter* described in the reports. However, one case had non-infective complications related to prematurity. The average antibiotic duration ranged between 10 and 14 days. Among the sixrecovered cases, two were treated with cefepime, 2 received a combination of aminoglycosides with carbapenem, one received ampicillin and gentamicin, and one received meropenem with colistin.There weremortalities in our review population. One was due to non-*R radiobacter*-related complications, and the other baby was reported to have died, though the direct relation to*R. radiobacter* was not mentioned; it is noteworthy that the isolate was sensitive only to levofloxacin, and the same was not administered to the baby.

LIMITATIONS

Our review had few limitations; we attempted to include all literature on neonatal infection caused by *R. radiobacter*, although several studies did not offer a complete description of the patients. Our minimal sample size made it difficult to generalise

our results, which was another downside.The strength of this study is that we attempted to analyse the limited literature extensively to help disseminate the information to help aid in the treatment of subsequent cases.

CONCLUSION

Our systematic review reveals the emerging significance of *R. radiobacter* as a human pathogen in neonates. While historically associated with compromised immunity and medical devices, our findings highlight its impact on otherwise healthy infants. The limited literature underscores the urgency for more extensive studies to comprehend the spectrum of *R. radiobacter* infections in neonates.After analysing eight neonatal cases, we noticed a wide range of clinical presentations, but the majority of them responded well to antibiotics. However, we were surprised by the antibiotic susceptibility patterns, which showed sensitivity to aminoglycosides and resistance to colistin, raising concerns. To fully understand the clinical implications, risk factors, and optimal treatment strategies for neonatal *R. radiobacter* infections, it is crucial to conduct larger prospective studies. Our review would signify the importance of early recognition and treatment of a condition that can sometimes be fatal. Further prospective studies are needed to understand this organism's clinical implications better.

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