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Review

Animal models of acute otitis media – A review with practical implications for laboratory research

N.H. Davidoss[a,*], Y.K. Varsak[b,c], P.L. Santa Maria[a,b,d,e]

[a] Department of Otolaryngology, Head and Neck Surgery, Sir Charles Gairdner Hospital, Nedlands, Australia
[b] Department of Otolaryngology, Head and Neck Surgery, Stanford University, Stanford, California, USA
[c] Department of Otolaryngology, Head and Neck Surgery, Necmettin Erbakan University, Konya, Turkey
[d] Department of Ear Sciences, The University of Western Australia, Crawley, Australia
[e] Department of Ear Sciences, Ear Science Institute Australia, Subiaco, Australia

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ABSTRACT

Considerable animal research has focused on developing new strategies for the prevention and treatment of acute otitis media (AOM). Several experimental models of AOM have thus been developed. A PubMed search of the English literature was conducted from 1975 to July 2016 using the search terms "animal model" and "otitis media" from which 91 published studies were included for analysis, yielding 123 animal models. The rat, mouse and chinchilla are the preferred animals for experimental AOM models with their individual advantages and disadvantages. The most common pathogens used to create AOM are *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. *Streptococcus pneumoniae* (types 3, 23 and 6A) and non-typeable *Haemophilus influenzae* (NTHi) are best options for inoculation into rat and mouse models. Adding viral pathogens such as RSV and Influenza A virus, along with creating ET dysfunction, are useful adjuncts in animal models of AOM. Antibiotic prophylaxis may interfere with the inflammatory response without a significant reduction in animal mortality.

1. Introduction

Acute otitis media (AOM) is a host's adaptive response to a most commonly, bacterial invasion of the middle ear (ME). The three most common bacterial causative agents of AOM in humans are *Streptococcus pneumoniae*, non-typeable *Haemophilus influenzae* (NTHi) and *Moraxella catarrhalis*, all of which are common commensal species of the paediatric nasopharynx (NP) [1,2]. Histologically, AOM is characterised by epithelial hyperplasia and metaplasia, subepithelial oedema, hyperaemia, focal haemorrhage, inflammatory cell infiltration and osteoneogenesis. An experimental environment in the animal ME should resemble the pathological setting found in the human ear. For this purpose, a variety of animal models has been developed. Experimental models of AOM in laboratory animals allow the study of histopathological changes of the ME during inflammation, the effect of antibiotics administered locally or systemically and the implantation of biomaterials in biocompatibility studies [3–9]. An animal model for AOM may also allow the testing of potential new treatments including antibiotics and vaccines [10–12]. Factors including the type of infectious agent, ME state and tubal clearance of secretions can influence the development and duration of an induced infection in an experimental model. In this paper, we are reviewing animal models of AOM considering the types of animals used, infectious pathogen, strain, delivery methods and mortality rates so that one can easily see the advantages and disadvantages of using different AOM animal models and select the best model for a proposed study.

A PubMed literature search was conducted from 1975 to July 2016 to identify relevant publications using the following specific search term – "animal model" and "otitis media". A total of 206 abstracts were found. Articles were assessed for relevance according to their title and abstract. Potentially relevant papers were retrieved in full text and critically appraised for relevance. Only articles in English were included. The bibliographies of publications identified as relevant were manually searched for potentially relevant titles and 110 additional publications were found. Only articles involving animal models of AOM were included. Articles involving animal models of otitis media with effusion (OME) or chronic otitis media were not included. Finally, 91 studies were included for

Abbreviations: AOM, acute otitis media; ME, middle ear; NTHi, non-typeable *Haemophilus influenzae*; OME, otitis media with effusion; ET, Eustachian tube

* Corresponding author at: Sir Charles Gairdner Hospital, Hospital avenue, Nedlands, 6009 WA, Australia.
E-mail address: nishantdavidoss@gmail.com (N.H. Davidoss).

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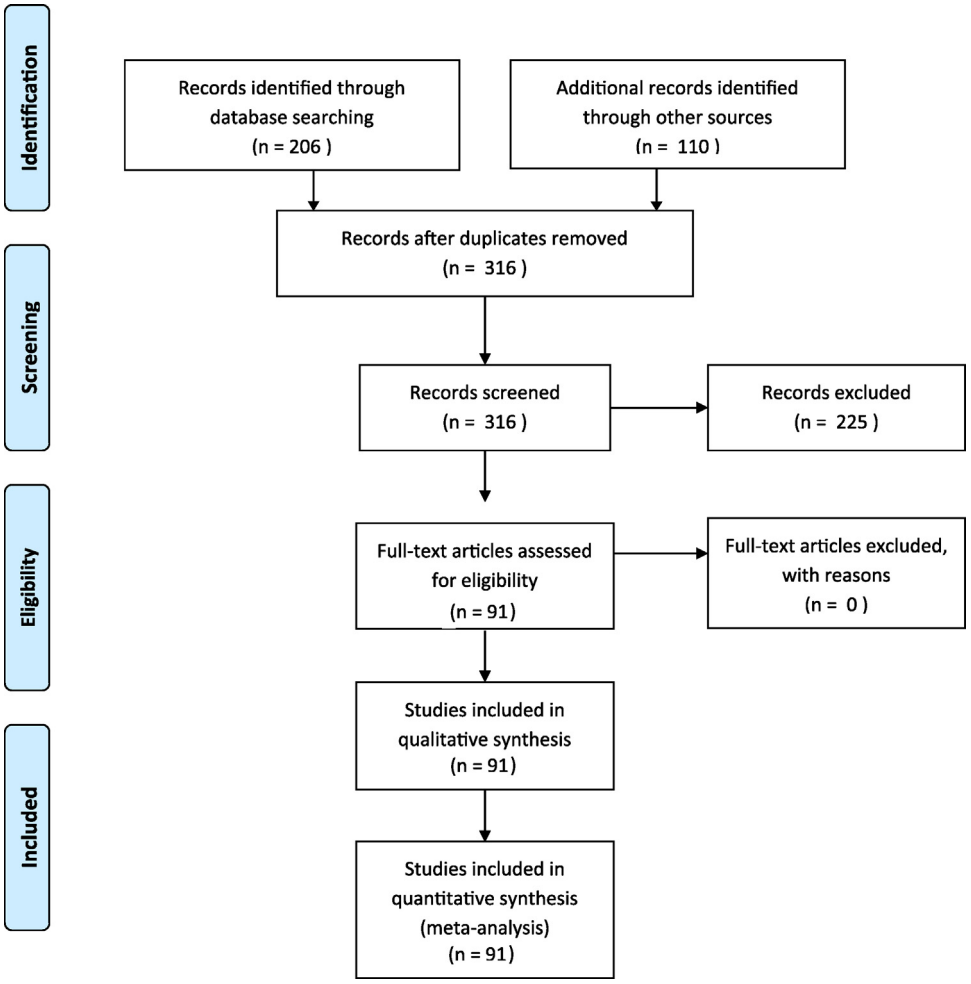

Fig. 1. The review strategy of the review summarised according to PRISMA guidelines [13].

analysis in this review, yielding 123 animal models. The review strategy is summarised according to PRISMA guidelines (Fig. 1) [13].

2. Discussion

The choice of antibiotics and mortality rates either from sepsis or surgical complications from the summarised studies in which animal models of AOM were used are presented in Table 1. The animal species, causative pathogen and delivery method have also been recorded. The chinchilla was the most common model organism, used in 50 animal models, followed by the rat in 39 animal models. Other model organisms included the mouse, gerbil and guinea pig (Table 2). The most common pathogen used was *Streptococcus pneumoniae*, used in 74 models, 4 of which were models where the bacteria was used in conjunction with a viral pathogen (Table 3). The transbullar inoculation approach, used in 78 models, was the most common delivery method (Table 4). Six animal models involved antibiotic administration. Animal mortality was low, but only reported in 17 of the 123 models included in this review.

There are several advantages of using animal models of AOM. Animal models possess many histological and pathological similarities with the human condition. It is also possible to extrapolate findings from these models to other transgenic and genetic models. Furthermore, the small physical size possessed by the majority of these animal species facilitates easy handling in laboratory settings. Animals used in the laboratory testing often possess predictable physiology, pharmacodynamics and pharmacokinetics which have been previously well researched. The disadvantages of using AOM animal models include the difficulty in creating the multifactorial environment of pathogenesis, difficulties in animal handling and manipulation of smaller sized tissues and in some cases the ease of developing sepsis.

2.1. Choice of animal

The rat is a favoured model for AOM as it has ME anatomy and histology of the highest compatibility with that of the human infant and child, as compared to other rodents [62]. Rats have MEs of similar histological cell types and ciliary clearance tracts to that of humans [97]. The rat Eustachian tube (ET) opening pressure corresponds to that in humans [98]. Rat MEs can also be readily infected with human pathogens [99]. The rat AOM course also closely resembles that of humans [5]. The relatively large tympanic bulla of the rat makes it easy to inoculate with bacteria into ME and once performed represents an infection which, like humans, is self-limiting (10–12 days) while preserving the TM and displaying no delayed signs of ME effusion [5,100]. Rats offer the substantial benefit of not being prone to develop general sepsis [100]. When inoculated appropriately, it is possible to produce a persistent OME which lasts for greater than 16 weeks [14].

The chinchilla is another favoured model in AOM research. Chinchillas are a large rodent and have TMs almost the same size as humans. They have a large bulla which facilitates ease of pathogen inoculation and subsequent collection of ME effusions [6]. Chin-

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