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Original Article

Differences in Antibiotic Resistance of MRSA Infections in Patients with Various Types of Otitis Media

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OBJECTIVES: We investigated the epidemiological and antibiotic resistance differences in methicillin-resistant *Staphylococcus aureus* (MRSA) infections in patients with otitis media with effusion (OME), acute otitis media (AOM), chronic suppurative otitis media (CSOM), and chronic cholesteatomatous otitis media (CCOM).

MATERIALS and METHODS: We conducted a retrospective study of patients with newly identified MRSA infections from January 2009 through January 2017. Overall, 3,522 patients from 10 tertiary referral hospitals were included in the study. An antibiotic sensitivity test was performed for each isolate.

RESULTS: MRSA infections in patients with CSOM and CCOM were more resistant to ciprofloxacin, clindamycin, erythromycin, gentamicin, levofloxacin, and tetracycline. Patients showed good susceptibility to rifampicin, trimethoprim/sulfamethoxazole (TMP/SMX), and vancomycin.

CONCLUSION: MRSA infections in various otitis media cases showed different resistance patterns. MRSA infections in patients with COM and CCOM were more resistant to antibiotics than those in patients with OME and AOM.

KEYWORDS: Methicillin resistance, *Staphylococcus aureus*, chronic suppurative otitis media, cholesteatoma, otitis media with effusion, acute otitis media

INTRODUCTION

Otitis media (OM) is a common bacterial infection, especially in children [1, 2]. Antibiotics have been the primary treatment for OM since the early 1950s [3]. OM is a frequent indication for antibiotic use, visits to outpatient clinics, and surgery [1, 4, 5]. Antibiotic usage is not well controlled, and broad-spectrum antibiotic use is increasing [5, 6]. Although several sets of guidelines have been developed to control antibiotic use in patients with OM [7, 8], the proper use of antibiotics for OM remains unclear [9, 10].

Several pathogens are responsible for this disease, especially in patients with perforation, cholesteatoma, and chronic OM (COM) [11, 12]. Since the first report of methicillin-resistant *Staphylococcus aureus* (MRSA) in 1961, the prevalence of this pathogen has increased. Although the bacteriology of MRSA has been investigated extensively, little is known about the differences in MRSA infections in various types of OM. OM with effusion (OME) and acute OM (AOM) are especially common in children, and frequent

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administration of antibiotics to children increases the likelihood of the emergence of antibiotic-resistant bacterial strains. AOM can progress to chronic suppurative OM (CSOM), which is associated with ear drum perforation and purulent discharge. Thus, antibiotic use in AOM and OME can affect the antibiotic resistance of COM. In addition, staphylococcal enterotoxins may be involved in the pathogenesis of chronic inflammatory diseases. However, the role of *S. aureus* in chronic inflammatory processes in OM has not yet been fully evaluated [13]. The present study therefore investigated the differences in the epidemiology and antibiotic resistance of MRSA strains isolated from patients with OME, AOM, CSOM, and chronic cholesteatomatous OM (CCOM), with the goal of optimizing treatment strategies in patients with OM infected with MRSA.

MATERIALS and METHODS

Patient Selection

This retrospective study included patients diagnosed with OM, AOM, or COM with/without cholesteatoma who visited the clinics of 10 university medical hospitals (10 tertiary referral hospitals) from January 2009 through January 2016. The study protocol was approved by the Institutional Review Board of Medical Center (IRB 2014-2695). Informed consent was waived owing to the retrospective design of the study. Data obtained from patients' medical records included age, gender, diagnosis, time of culture, and antibiotic susceptibility. Patients with incomplete medical records were excluded from the study.

Types of OM were diagnosed according to clinical practice guidelines [14]. OME was diagnosed by the presence of fluid in the middle ear on otoscopy or tympanometry (Grason–Stadler GSI 33 Middle Ear Analyzer; Viasys, Conshohocken, PA, USA). Diagnostic findings of pneumatic otoscopy and otomicroscopy considered positive for OME included tympanic membrane dullness, impaired mobility, an air-fluid level or bubble, or a type B or C tympanogram. AOM was diagnosed by the presence of acute symptoms, such as otalgia and fever, along with fluid in the middle ear. CSOM was diagnosed by the presence of a non-intact tympanic membrane and otorrhea for >3 months. CCOM was diagnosed when cholesteatoma was histologically confirmed or otoscopically observed with a pocket with skin debris. Patients with congenital cholesteatoma were also excluded from the study.

Culture Methods

A sterile ear speculum was inserted into the infected ear, and the otorrhea was swabbed with a disposable commercial transport swab. In the absence of otorrhea, fluid aspirated from the middle ear was cultured in a sterile bottle.

Antimicrobial sensitivity was evaluated by agar diffusion methods according to the guidelines of the National Committee for Clinical Laboratory Standards. The sensitivity results following antibiotic treatment were collected from the original laboratory records. Antibiotics tested included ampicillin, ciprofloxacin, clindamycin, erythromycin, gentamicin, levofloxacin, linezolid, oxacillin, penicillin G, rifampicin, teicoplanin, tetracycline, TMP/SMX, and vancomycin.

Statistical Analysis

Results are expressed as mean±standard deviation or percentage (%). Gender was compared by χ^2 tests and age by t-tests. Pearson's χ^2 test was used for comparisons of antimicrobial resistance. All statistical analyses were performed using The Statistical Package for the Social Sciences (SPSS) software version 21.0 (IBM Corp.; Armonk, NY, USA). A p-value of <0.05 was considered statistically significant.

RESULTS

During the study period, 3,522 consecutive patients (1,591 males and 1,931 females; age range, 1-81 years) were diagnosed with OM. Of the patients, 3,135 (1,426 males and 1,709 females; age range, 1-78 years) were negative for MRSA, and 387 (165 males and 222 females; age range, 1-81 years) were positive for MRSA. The overall prevalence of MRSA in the study sample was 10.99%. The prevalences of MRSA in patients with OME, AOM, COM, and CCOM were 6.26%, 6.83%, 12.68%, and 11.38%, respectively (Table 1).

Among patients diagnosed with OME and AOM, those infected with MRSA were older than those without MRSA, whereas those without MRSA with COM and CCOM were older than those with MRSA, but these differences were not statistically significant. The percentage of males was higher among patients without MRSA, whereas that of females was higher among those with MRSA, but the difference was not statistically significant. The percentage of females was higher among all subgroups of patients infected with non-MRSA, except for those with OME. Among patients with MRSA, only those diagnosed with CCOM showed a male predominance. None of these gender differences between MRSA and non-MRSA groups, however, were statistically significant.

Methicillin-resistant *Staphylococcus aureus* strains isolated from all four groups of patients with OM showed poor responses to ampicillin, oxacillin, and penicillin G. Strains of MRSA from patients with OME showed good responses to most antibiotics. The antibiotic susceptibilities of MRSA strains were lower in patients with OME and AOM than in those with COM and CCOM. Strains from patients with CCOM had the poorest responses to all antibiotics. The antibiotic susceptibilities of strains were lower in patients with AOM than in those with OME, except for ciprofloxacin and erythromycin. Strains from patients with OME and AOM showed moderate responses to ciprofloxacin, clindamycin, erythromycin, and gentamicin. Responses to tetracycline were low in strains from patients with AOM. Responses to ciprofloxacin, clindamycin, erythromycin, gentamicin, levofloxacin, and tetracycline were significantly lower in strains from patients with COM and CCOM than in those from patients with OME and AOM. Strains from all groups showed excellent susceptibility to rifampicin and TMP/SMX, but were slightly lower in strains from patients with COM and CCOM. None of the strains tested showed resistance to linezolid, teicoplanin, or vancomycin (Table 2).

DISCUSSION

The present study showed that MRSA strains isolated from patients with OME, AOM, CSOM, and CCOM differed in antibiotic resistance. MRSA infections in patients with CSOM and CCOM were more resistant to ciprofloxacin, clindamycin, erythromycin, gentamicin, levofloxacin, and tetracycline, with strains from patients with CCOM showing the highest resistance. Strains from all patients showed good susceptibility to rifampicin, TMX/SMX, and vancomycin. Antibiotic resistance has expanded worldwide, with Asia, especially South Korea, having much higher antibiotic resistance rates than other regions [15].

Table 1. Demographic and clinical characteristics of patients with otitis media infected with MRSA and non-MRSA strains

	Group	OME	AOM	COM	CCOM	Total
Cases	Non-MRSA	584	191	1,838	522	3,135
	MRSA	39	14	267	67	387
Prevalence		6.26 (39/623)	6.83 (14/205)	12.68 (267/2,105)	11.38 (67/589)	10.99 (387/3,522)
Mean age, years (range)	Non-MRSA	16.64±22.26	30.32±26.45	51.33±17.57	46.91±17.66	53.55±23.00
	MRSA	28±26.48	39.5±28.73	48.42±17.10	45.52±16.36	45.76 (0–81)
p		0.001	0.764	0.571	0.642	
Gender (M:F)	Non-MRSA	324:260	86:105	760:1,078	256:266	1,426:1,709
	MRSA	17:22	3:11	108:159	37:30	165:222
p		0.149	0.086	0.780	0.341	

MRSA: methicillin-resistant Staphylococcus aureus; OME: otitis media with effusion; AOM: acute otitis media; COM: chronic otitis media; CCOM: chronic cholesteatomatous otitis media

Table 2. Antibiotic susceptibility of MRSA strains isolated from patients with OME, AOM, COM, and CCOM

Drug	OME no. (%)	AOM no. (%)	COM no. (%)	CCOM no. (%)	p
Ampicillin	0/22 (0)	0 (N/A)	0/129 (0)	0/29 (0)	<0.001
Ciprofloxacin	16/39 (41.02)	6/14 (42.86)	36/266 (13.53)	5/66 (7.58)	<0.001
Clindamycin	15/39 (61.53)	8/14 (57.14)	49/262 (18.7)	10/67 (14.93)	<0.001
Erythromycin	15/39 (38.46)	6/14 (42.86)	39/267 (14.6)	7/67 (10.45)	<0.001
Gentamicin	23/39 (58.97)	6/14 (42.86)	77/266 (28.95)	14/66 (21.21)	<0.001
Levofloxacin	9/21 (42.86)	1/1 (100)	18/127 (14.17)	4/31 (12.9)	0.002
Linezolid	27/27 (100)	14/14 (100)	239/239 (100)	62/62 (100)	
Oxacillin	0/39 (0)	0/14 (0)	0/267 (0)	0/67 (0)	
Penicillin G	1/38 (2.6)	0/14 (0)	0/213 (0)	0/63 (0)	
Rifampicin	9/9 (100)	14/14 (100)	148/156 (94.87)	33/38 (86.84)	
Teicoplanin	39/39 (100)	14/14 (100)	267/267 (100)	67/67 (100)	
Tetracycline	19/39 (48.7)	4/14 (28.57)	58/250 (23.2)	10/65 (15.38)	0.001
TMP/SMX	37/38 (97.4)	14/14 (100)	261/266 (98.12)	60/67 (89.55)	0.005
Vancomycin	39/39 (100)	14/14 (100)	267/267 (100)	67/67 (100)	

N/A: not available.
MRSA: methicillin-resistant Staphylococcus aureus; OME: otitis media with effusion; AOM: acute otitis media; COM: chronic otitis media; CCOM: chronic cholesteatomatous otitis media; TMP/SMX: trimethoprim/sulfamethoxazole
p<0.05 was considered statistically significant.

S. aureus is a Gram-positive coccus causing skin infections, such as abscesses and wound infections, and various diseases, such as sepsis and toxic shock syndrome, as well as being a common pathogen in infectious diseases in otolaryngology. It is the Gram-positive coccus most frequently isolated from clinical specimens, as well as being isolated from approximately 40% of noses of healthy adults. It can be transmitted by skin-to-skin contact and is a major pathogen of nosocomial infections, such as surgical-site infection and pneumonia [16].

Methicillin-resistant *Staphylococcus aureus* is highly resistant to multiple antibiotics. It is the second most common pathogenic bacteria in COM, following *Pseudomonas* [17]. MRSA infections in patients with COM are hard to eradicate owing to their resistance to many antibiotics. Moreover, it is difficult to control inflammation despite constant treatment with antibiotics and irrigation of the middle ear cavity. Care is required during surgery to remove inflammation not only because of MRSA-induced otorrhea but also because of mucosal edema in the middle ear or mastoid cavity and granuloma formation, and postoperative complications may occur. MRSA has been reported to be more frequent in patients with COM than in those with acute otitis externa and myringitis and to be more frequent in patients with suppurative OM than in those with acute tonsillitis and peritonsillar abscess. Thorough sterilization of instruments and hygiene control for healthcare professionals should be emphasized in the treatment of otorrhea [18].

Methicillin-resistant *Staphylococcus aureus* should be considered when antibiotic treatment fails in patients with OM. Antibiotic control in children may affect antibiotic resistance in adults. Bacterial cultures from

children showed greater antibiotic sensitivity than those from adults, suggesting that differences in antibiotic resistance may be related to age [19]. Recurrent infection can also change antibiotic sensitivity. For example, recurrence of OME can alter sensitivity to antibiotics, especially to penicillin and erythromycin [20]. Previous antibiotic use in patients with otitis externa has been associated with increased antibiotic resistance, and highly resistant bacteria have been associated with higher rates of treatment failure [21]. In the present study, patients infected with MRSA with OME and AOM were older than those infected with non-MRSA strains, although the difference was statistically significant only in patients with OME. Additionally, patients infected with non-MRSA with COM and CCOM were older than those infected with MRSA, indicating that age per se was not a risk factor for MRSA. History of antibiotic use or hospitalization may be more important. However, since this retrospective study was conducted in tertiary hospitals, bacteria may have been present in culture-negative patients prior to antibiotic use because patients with OM with otorrhea had a history of antibiotic use before hospital admission; thus, some culture-negative patients may have been culture-positive. Additionally, surgery for COM can change the bacterial culture results [22].

The present study also found no difference in gender between patients infected with MRSA and non-MRSA strains. OME is more common in boys [5, 14], a finding that is consistent with our results. Although patients infected with MRSA with CCOM showed a female predominance, this difference was not statically significant (p=0.149).

Knowing MRSA resistance patterns to antibiotics is important for disease control. MRSA strains show low sensitivity to other antibiotics. For example, 100% of MRSA strains isolated from patients with AOM were resistant to penicillin, tetracycline, cefoxitin, and erythromycin [11]. However, most MRSA strains were highly sensitive to vancomycin, teicoplanin, and TMP/SMX [23]. Our MRSA strains also showed 100% responses to linezolid, teicoplanin, and vancomycin and high responses to TMP/SMX and rifampicin.

Although MRSA infections occur mainly in adults and children who are hospitalized or have been receiving medical treatment for a long period, they have been frequently detected in community-acquired infections. Two types of MRSA have been isolated from patients with OM: community-acquired (CA) and hospital-acquired (HA) MRSA [24]. The incidence of CA MRSA in patients with COM has risen markedly over the past decade, with CA MRSA and HA MRSA in patients with COM differing clinically and microbiologically [25]. CA MRSA was found to show good susceptibility to vancomycin, teicoplanin, fusidic acid, and minocycline [26], and TMP/SMX was reported to be a good topical agent for patients with AOM with otorrhea infected with CA MRSA [27]. MRSA showed low susceptibilities to commonly used otic drops, such as gentamicin and ciprofloxacin, whereas CA MRSA showed good susceptibility to TMP/SMX and fusidic acid [24]. Thus, a careful review of culture results is required to determine whether an MRSA strain is CA or HA and to choose the appropriate antibiotic. Since the MRSA strains in our study showed good susceptibility to TMP/SMX, most were likely CA MRSA. Additionally, genetic analyses of MRSA strains isolated from Korean patients with COM showed that most were CA [28].

We found that MRSA strains isolated from patients with CCOM had the poorest responses. Cholesteatoma is a cause of recurrent or intractable OM, usually requiring multiple surgical operations and/or hospital admission [29, 30]. Additionally, the biofilm in cholesteatomas may contribute to their wide resistance to antibiotics [31, 32]. The mechanisms of action of different classes of antibiotics differ, making it necessary to understand the structural features of bacteria, such as their cell walls. Antibiotics may inhibit bacterial metabolism, including inhibiting the synthesis of cell walls, proteins, and nucleic acids. Alternatively, antibiotics may inhibit bacterial activities or folate or may transform cell membranes and structures [33].

Although all strains of MRSA responded to linezolid, teicoplanin, and vancomycin, these drugs are expensive and require hospitalization or injection. Moreover, vancomycin and teicoplanin consist of macromolecules, requiring intravenous administration. Vancomycin is especially problematic as it can induce anaphylactic reactions, such as hypotension, dyspnea, and pruritus, and complications, such as *Clostridium difficile* infection, hearing and vestibular disorders, neutropenia, and vasculitis. Additionally, limited use can prevent the development of resistance to these drugs. Rifampicin and TMP/SMX can be used in outpatients and are inexpensive; therefore, they may be good initial candidates for antibiotic treatment.

The limitations of our study include its retrospective design and the relatively small number of MRSA-positive patients available for statistical analysis. Despite these limitations, these results add to existing knowledge regarding MRSA infections in OM. Additional research on MRSA in patients with OM may prevent the spread of antibiotic-resistant strains.

CONCLUSION

Methicillin-resistant *Staphylococcus aureus* infections in various otitis media cases showed different resistance patterns. MRSA infections in patients with COM and CCOM were more resistant to antibiotics than those in patients with OME and AOM.

Ethics Committee Approval: Ethics Committee Approval was received for this study from the Ethics Committee of Kyung Hee University Hospital (IRB No. KMC IRB 1431-03).

Informed Consent: Informed consent was exempted by the board.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.G.Y.; Design – M.K.P., S.G.Y.; Supervision- M.G.K., J.E.J.; Resource- B.J.Y., H.S.M.; Materials – B.C.H., M.G.K.; Data Collection and/or Processing- K.S.H., N.D.W.; Analysis and/or Interpretation – N.D.W.; Literature Review – L.H.W.; Writing – M.K.P., N.D.W.; Critical Review – S.G.Y., K.S.H.

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Conflict of Interest: The authors have no conflict of interest to declare.

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