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Systematic Review

Bacterial Etiology of Lower Respiratory Tract Infections in Turkey: A Systematic Review

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Abstract

Context: Lower respiratory tract infections (LRTIs) are prevalent diseases and a major cause of referral to primary healthcare centers. The present study aimed to identify the bacterial etiology of LRTIs to determine the trend changes within the past three decades and help ascertain the new scenarios of empirical LRTI therapy in Turkey.
Methods: This systematic review was conducted by searching various electronic databases based on specified criteria. In total, 2,670 articles were identified, which had been published during 1990 - 2020 and could be potentially used, and 46 scientific studies that met the eligibility criteria were selected for the review.
Results: The most frequently isolated bacteria in the reviewed studies were *Acinetobacter* spp. (31.68%), *P. aeruginosa* (16.59%), *H. influenzae* (14.30%), and *S. pneumoniae* (13.80%). Data analysis also indicated that the most frequent reports of LRTI agents were in Aegean region in Turkey during 2014-2020.
Conclusions: This systematic review reflected the changes in LRTI agents over the past three decades in Turkey. Knowledge of the frequency of LRTI bacterial agents specific to each country could help healthcare professionals in reporting laboratory results and prescribing/selecting the most effective antibiotics for the treatment of the disease.

Keywords: Lower Respiratory Tract Infections, Community-Acquired Pneumonia, Nosocomial Pneumonia

1. Context

Lower respiratory tract infections (LRTIs) are prevalent diseases and a major cause of referral to primary healthcare centers. Antibiotics are mostly prescribed for the treatment of these disorders as bacterial pathogens are considered to be the most common etiological factors that induce LRTIs (1, 2).

The diagnosis and treatment of LRTIs require a multidisciplinary approach that integrates current clinical, microbiological, and immunological data. Such an approach is essential due to the large number of the etiological factors that cause these infections, the unfavorable symptoms caused by particular pathogens, the increasing number of antibiotic-resistant bacteria, and limited microbiological diagnostic capabilities (3). Physicians may not routinely opt for etiologic diagnoses and prefer a therapeutic approach based on the distribution of pathogens and previous epidemiological findings (4).

The early and accurate identification of etiological agents is the most effective approach to avoiding inappropriate antibiotic use (5). The first-line treatment for LRTIs should be planned in accordance with national recommendations on appropriate antibiotics, as well as the spectrum of the common pathogens and resistance patterns in a specific region (6).

2. Objective

The present study aimed to identify the bacterial etiology of LRTIs, determine the trend of changes within the past three decades, and help ascertain the new empirical LRTI therapy scenarios in Turkey.

3. Methods

This systematic review was conducted in four phases of data sources and keywords, qualitative analysis of studies, determination of eligibility criteria, and data analysis.

3.1. Data Sources and Keywords

A systematic review was performed via searching in databases such as PubMed, Turkish Medline, Scopus, EB-

SCO, Google Scholar, and other indexed journals using keywords such as lower respiratory tract infections, lower respiratory tract infections in Turkey, respiratory tract infections in Turkey, and alt solunum yolu enfeksiyonları Türkiye.

3.2. Eligibility Criteria

The eligibility criteria of the articles were the scientific studies conducted in Turkish or English language, studies performed in Turkey, and studies presenting consistent data. The exclusion criteria were unavailable full texts, data on lower respiratory tract infections, data on the infections between upper/lower respiratory tracts without distinction, assessment of fewer than 10 specimens, and lack of detailed description. Based on the screening criteria, 46 studies were selected for our systematic review. Figure 1 depicts the flowchart of the systematic review.

3.3. Data Analysis

Data were divided into five groups based on the publication year of the selected studies, including 1990 - 1995, 1996 - 2001, 2002 - 2007, 2008 - 2013, and 2014 - 2020. Two independent researchers analyzed the data, and disagreements were resolved unanimously in line with the eligibility criteria. Data were collected on the name of the first author, study area, total number of isolates, methodologies, characteristics of the patient population, and prevalence of LRTI agents. In addition, tables were drawn to demonstrate the prevalence data in terms of numbers, so that the selected studies could be assessed by a common unit.

4. Results

The literature search based on the eligibility criteria resulted in 2,670 articles, which had been published during 1990 - 2020 and could be potentially used, and 46 scientific studies meeting the eligibility criteria were selected for the final review (Table 1). Frequencies were determined by the analysis of the data on LRTI agents reported in different studies.

According to the findings, the most commonly isolated bacteria were *Acinetobacter* spp. (31.68%), *P. aeruginosa* (16.59%), *H. influenzae* (14.30%), and *S. pneumoniae* (13.80%). Table 2 shows the frequency of the isolated bacterial species by years. Accordingly, *S. pneumoniae* was the most common bacterial species isolated during 1990 - 1995, *M. catarrhalis* was mostly frequently isolated during 1996 - 2001, *S. aureus* was most commonly isolated during 2002 - 2007 and 2008 - 2013, and *A. baumannii* was most frequently isolated during 2014 - 2020.

The findings of the current review indicated significant changes in the reported LTRI data over time, which could be associated with the increased prevalence of *A. baumannii* infections. Furthermore, a three-fold increase was observed in the data of *A. baumannii* infections, especially within the past seven years. On the other hand, the reports on *P. aeruginosa* infections have decreased (Table 2).

Sputum, tracheal aspirate (TA), endotracheal aspiration (ETA), and bronchoalveolar lavage (BAL) have been the most commonly used samples in the diagnosis of LRTI. Table 3 shows the frequency of bacterial isolation and the clinical sample table correlations. In terms of isolation frequency, *A. baumannii* has been isolated from TA, sputum, BAL, and ETA samples, *P. aeruginosa* and *K. pneumoniae* have been isolated from BAL and sputum samples, and *S. pneumoniae* and *H. influenzae* have been the most frequently isolated agents from sputum samples.

Table 4 shows the distribution of the isolated infectious agents by geographical regions. Data are scarce on nosocomial LRTI agents in the Black Sea region. Moreover, sufficient data could not be found regarding LRTI agents in the Southeastern Anatolia region. The Aegean region has also been the geographical area with the highest number of notifications on LRTI agents. *S. pneumoniae* and *H. influenzae* are community-acquired LRTI agents detected in all regions. Furthermore, nosocomial agents such as *A. baumannii*, *P. aeruginosa*, *K. pneumoniae*, and *S. aureus* have been frequently reported. The overall analysis of data indicated that LRTI agents were most commonly reported in the Aegean region during 2014 - 2020.

5. Discussion

The etiological diagnosis of LRTIs, which is a major cause of mortality and morbidity, is essential to the treatment of the disease. The distribution of LRTI etiological agents may vary depending on the geographical region, season, age, ethnicity, and underlying diseases (53). LRTIs have changed during the COVID-19 outbreak, which is currently the most pressing public health concern. Consequently, community-acquired and nosocomial LRTI bacterial agents have been extensively investigated due to the risk of developing secondary infections and the essential differences between the treatment of the viral and bacterial agents that cause LRTIs. Therefore, determining possible LRTI pathogens through large-scale studies is of utmost importance in the planning of empirical treatments (54).

According to the studies evaluated in our systematic review, the most common community-acquired LRTI agents were *S. pneumoniae* and *H. influenzae*, while the most common nosocomial LRTI agents were *A. baumannii*, *P. aeruginosa*, *K. pneumoniae*, and *S. aureus*. Changes in the fre-

Table 1. Data of Reviewed Studies

Author	Year	City	N	Bacterial Species	Comorbidities	Clinics
Kurt et al. (7)	1990	Ankara	16	*H. influenzae, S. pneumoniae*	1 LA, 6 pneumonia, 5 bronchiectasis, 4 bronchiectasis + COPD	-
Saka et al. (8)	1994	Ankara	85	*S. pneumoniae*	24 COPD, 3 COPD + 13 DM, COPD + CP, 8 bronchiectasis, 2 APT, 2 IPT, 11 pneumonia, 1 pneumonia + PE, 1 LA, 18 LC, 1 LC + DM, 5 BA, 2 DIF, 1 DL	-
Berkiten et al. (9)	1994-1997	İstanbul	291	*H. influenzae*	-	-
Koseoglu et al. (10)	1996	Ankara	24	*S. pneumoniae, H. influenzae, B. catarrhalis*	27 COPD, 13 BA, 7 bronchiectasis, 7 CB, 2 LC, 1 emphysema	
Ceylan et al. (11)	1996	İzmir	60	*P. aeruginosa, K. pneumoniae, Enterobacter* spp.	29 COPD, 25 CAP, 12 HAP	
Berkiten et al. (12)	1997	İstanbul	34	*S. pyogenes*	-	
Yurdakul et al. (13)	1997	Ankara	514	*S. pneumoniae, P. aeruginosa, S. aureus, K. pneumoniae, M. catarrhalis*	-	ICU
Senol et al. (14)	1999	İzmir	365	*S. pneumoniae, H. influenzae, M. catarrhalis*	-	ICU, Outpatient
Aydın et al. (15)	1999	Sivas	35	*S. pneumoniae*	35 COPD	-
Coplu et al. (16)	1999	Ankara	64	*H. influenzae*	33 CF	Outpatient
Aktepe et al. (17)	2000	Ankara	288	*H. influenzae, P. aeruginosa, S. aureus*	288 CF	-
Ünel et al. (18)	2000	İstanbul	100	*H. influenzae, M. catarrhalis, S. pneumoniae, Pseudomonas* spp.	100 COPD	-
Berkiten et al. (19)	2001	İstanbul	102	*S. pyogenes*	-	-
Erdogan et al. (20)	2001-2002	İstanbul	466	*H. influenzae, H. parainfluenzae, S. pneumoniae, M. catarrhalis, MSSA*	-	-
Talay et al. (21)	2002	İstanbul	41	*S. pneumoniae, K. pneumoniae, P. aeruginosa, E. coli*	17 COPD, 25 pneumonia	inpatient
Ciragil et al. (22)	2002	İstanbul	59	*P. aeruginosa*	59 CF	ICU, inpatient
Azap et al. (23)	2002	Ankara	77	*S. pneumoniae*	COPD, CAP	ICU, inpatient, Outpatient
Gonlugur et al. (24)	2004	Sivas	355	*Klebsiella* spp., *E. coli, Proteus* spp., *Enterobacter* spp., *A. baumannii, Serratia* spp.	NRI	ICU, inpatient, Outpatient
Gurol et al. (25)	2004	İstanbul	44	*S. pneumoniae*	-	-
Arikan Akan et al. (26)	2005-2007	Ankara	25	*A. baumannii, K. pneumoniae*	-	ICU, inpatient,
Atasever et al. (27)	2006	İzmir	837	*S. aureus, M. catarrhalis, H. influenzae, P. aeruginosa, S. pneumoniae, K. pneumoniae, E. coli, Acinetobacter baumannii, Enterobacter* spp.	837 LC, 535 pneumonia, 515 COPD	ICU, inpatient, Outpatient
Komus et al. (28)	2006	İzmir	16	*P. aeruginosa*	16 bronchiectasis	-
Uncu et al. (29)	2007	Ankara	82	*S. pneumoniae, H. influenzae*	-	-
Demir et al. (30)	2007-2010	Trabzon	78	*P. aeruginosa*	-	inpatient
Bayram et al. (31)	2007-2010	Van	191	*A. baumannii*	-	ICU, inpatient
Gazi et al. (32)	2008	Manisa	835	*Pseudomonas* spp., *Acinetobacter* spp., *Klebsiella* spp., *E. coli, S. maltophilia, Enterobacter* spp., S. marcescens	-	ICU, inpatient
Eksi et al. (33)	2008	Gaziantep	116	*S. pneumoniae*	-	ICU, inpatient, Outpatient
Kume et al. (34)	2008-2010	İzmir	175	*Acinetobacter* spp., *Pseudomonas* spp.	33 pneumonia, 40 COPD, 12 LC	ICU,
Akin et al. (35)	2009	Konya	62	*S. pneumoniae, H. influenzae, M. catarrhalis*	62 COPD	-
Ince et al. (36)	2009	Duzce	98	*M. catarrhalis, S. pneumoniae, H. influenzae, P. aeruginosa, E. coli*	98 COPD	ICU, inpatient, Outpatient
Bacakoglu et al. (37)	2009	İzmir	37	*A. baumannii*	8 COPD, 10 CAP, 1, pyopneumothorax, 1 LC	ICU,
Beşli et al. (38)	2012-2014	İstanbul	586	*S. pneumoniae, H. influenzae*	-	-
Özer et al. (39)	2012-2014	Hatay	1516	*A. baumannii, P. aeruginosa, K. pneumoniae, E. coli, S. aureus, Enterobacter cloacae, Streptococcus pneumoniae, Stenotrophomonas marcescens*	-	ICU, inpatient,
Akkoyun Bilgi et al. (40)	2013	İstanbul	163	*H. influenzae, S. pneumoniae, P. aeruginosa*	-	ICU, inpatient, Outpatient
Bayramoglu et al. (41)	2014	Trabzon	67	*S. pneumoniae, M. catarrhalis, H. influenzae*	-	-
Direkel et al. (42)	2015	Mersin	277	*A. baumanniii*		
Savcı et al. (43)	2015	Ankara	67	*A. baumanniii*	-	-
Alışkan et al. (44)	2016	Adana	184	*S. Pneumoniae,H. İnfluenzae*	-	-
Eroğlu et al. (45)	2016	Samsun	1183	*A. baumanniii*	-	ICU, inpatient, Outpatient
Aydemir et al. (46)	2016	Sakarya	130	*A. baumannii, K. pneumoniae, E. coli, S. aureus, E. cloacae, P. aeruginosa*	-	ICU
Maçin et al. (47)	2017	Ankara	130	*P. aeruginosa*	-	-
Sagmak-Tartar et al. (48)	2017	Elazığ	535	*A. baumanniii, P. aeruginosa, K. pneumoniae*	-	ICU
Kahraman et al. (49)	2017	Sakarya	71	*K. pneumoniae*	-	-
Altun et al. (50)	2018	Ankara	52	*S. pneumoniae*	-	-
Tanriverdi et al. (51)	2019	Samsun	330	*H. influenzae, M. catarrhalis, M. catarrhalis, S. Pneumoniae*	-	ICU, inpatient, Outpatient
Altay Koçak et al. (52)	2019	Adana	181	*A. baumannii, Klebsiella* spp., *P. aeruginosa, E. coli, H. influenzae, S. aureus, S. pneumoniae*	-	ICU, inpatient

Abbreviations: LA, lung abscess; DM, diabetes mellitus; CP, cor pulmonale; APT, active pulmonary tuberculosis; IPT, inactive pulmonary tuberculosis; PE, pleural effusion; LC, lung cancer; BA, bronchial asthma; DIF, diffuse interstitial fibrosis; DL, destroyed lung; CB, chronic bronchiectasis; CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia; CF, cystic fibrosis; NRI, nosocomial respiratory infections; ICU, intensive care unit.

Table 2. Total Frequencies of Bacterial Isolates by Year (N)

	Interval				
	1990 - 1995	**1996 - 2001**	**2002 - 2007**	**2008 - 2013**	**2014 - 2020**
***Acinetobacter* spp.**	0	0	81	872	2,024
B. catarrhalis	0	3	0	0	0
E. coli	0	5	98	142	78
***Enterobacter* spp.**	0	4	94	32	12
H. influenzae	4	227	298	380	435
K. pneumoniae	0	25	152	147	318
M. catarrhalis	0	345	0	56	0
P. aeruginosa	0	220	270	760	308
***Proteus* spp.**	0	0	10	0	0
S. aureus	0	70	315	37	55
S. maltophilia	0	0	0	42	0
S. pneumoniae	112	290	118	288	489
***Serratia* spp.**	0	0	6	21	0
Total	116	1,189	1,442	2,777	3,719

Table 3. Total Frequencies of Bacterial Isolates by Sample Type (N)

	Sample Type									
	TA	**S**	**BAL**	**DTA**	**ETA**	**PF**	**US**	**BA**	**TS**	**PE**
A. baumannii	1,339	536	330	115	319	206	129	0	3	0
B. catarrhalis	0	3	0	0	0	0	0	0	0	0
E. coli	59	96	78	0	36	29	23	0	0	0
***Enterobacter* spp.**	11	23	10	0	28	61	9	0	0	0
H. influenzae	256	680	186	6	0	182	0	34	0	0
H. parainfluenzae	0	17	0	0	0	0	0	0	0	0
K. pneumoniae	95	218	99	17	0	121	64	0	0	16
M. catarrhalis	113	112	36	0	0	135	0	3	0	0
P. aeruginosa	200	787	102	94	87	198	82	0	0	0
***Proteus* spp.**	0	10	0	0	0	0	0	0	0	0
S. aureus	52	105	133	29	0	158	0	0	0	0
S. maltophilia	0	0	0	0	0	0	42	0	0	0
S. pneumoniae	173	533	170	61	0	167	0	67	96	0
S. pyogenes	2	34	100	0	0	0	0	0	0	0
***Serratia* spp.**	0	27	0	0	0	0	0	0	0	0
Total	2,300	3,181	1,244	322	470	1,257	349	104	99	16

Abbreviations: TA, tracheal aspirate; S, sputum; PF, pleural fluid; BAL, bronchoalveolar lavage; DTA, deep tracheal aspiration; ETA, endotracheal aspiration; BA, bronchial aspiration; TS, throat swab; PE, pleural effusion; US, unspecified.

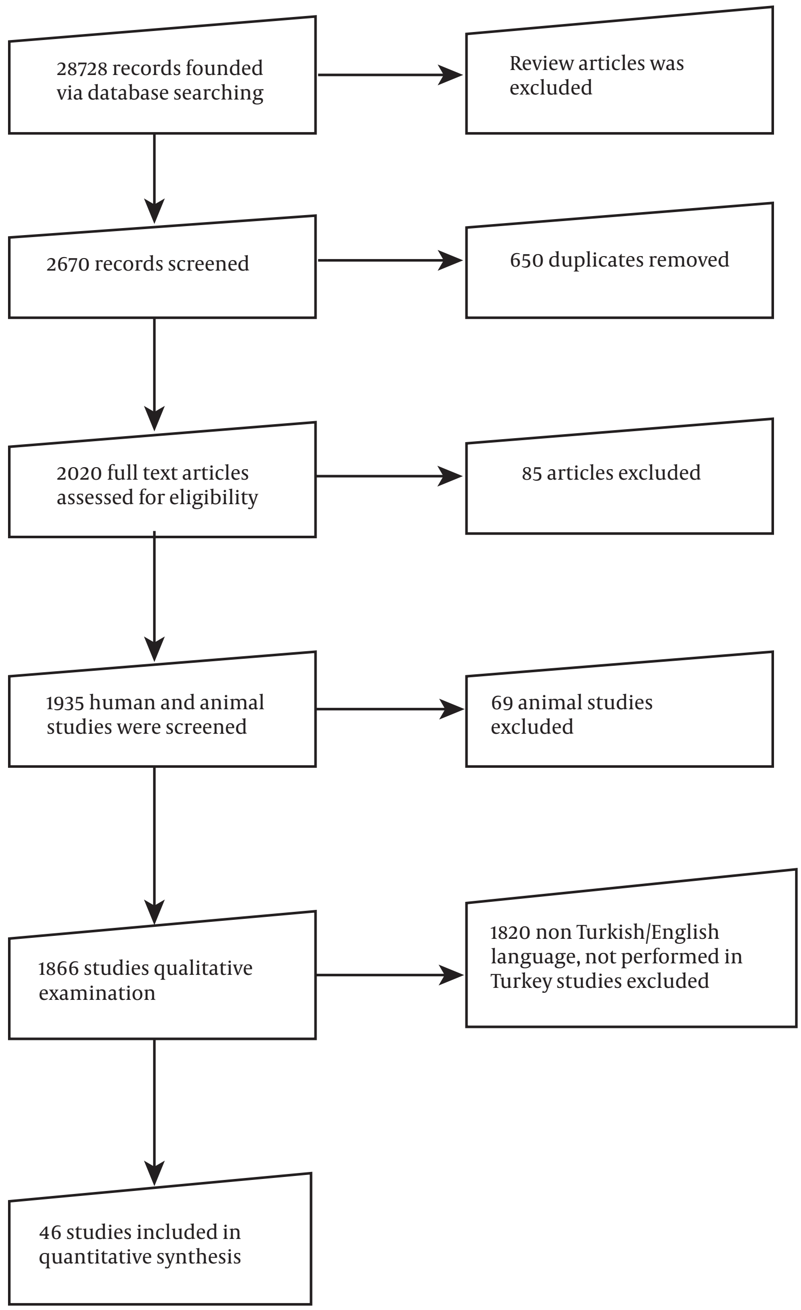

Figure 1. Flowchart of systematic review

quency of LRTI agents may be affected by factors such as the identification method, type of isolation samples, waiting times/conditions of sampling, healthcare professionals collecting the samples from the patients, interpretation of the results, and the principles of the automated devices.

Our observations indicated that researchers' trends are one of the critical factors affecting the distribution and frequency of LRTI pathogens (Table 4). The regional distribution of the studies showed that they were mostly performed in the Aegean region, and limited data were provided on the Southeastern Anatolia, as well as on the noso-

Table 4. Total Frequencies of Bacterial Isolates by Geographical Region in Turkey (N)

	Marmara	Mediterranean	Central Anatolia	Eastern Anatolia	Southeastern Anatolia	Aegean	Black Sea
A. baumannii	123	717	61	1,764	0	312	0
B. catarrhalis	0	0	3	0	0	0	0
E. coli	21	141	18	0	0	140	3
***Enterobacter* spp.**	18	16	10	0	0	98	0
H. influenzae	457	161	151	30	0	265	280
K. pneumoniae	130	172	49	101	0	190	0
M. catarrhalis	41	0	24	0	0	281	55
P. aeruginosa	151	296	286	127	0	597	101
***Proteus* spp.**	0	0	10	0	0	0	0
S. aureus	38	72	52	0	0	315	0
S. maltophilia	0	0	0	0	0	42	0
S. pneumoniae	274	192	506	55	21	137	130
***Serratia* spp.**	0	9	6	0	0	12	0
Total	1,253	1,776	1,176	2,077	21	2,389	569

comial LRTI pathogens in the Black Sea region. On the other hand, the distribution of these factors may be attributed to the used antibiotics, pathogen resistance, accompanying diseases, diagnostic techniques used in hospitals, and hospitals' development, climate, and sanitation state.

Once the COVID-19 pandemic is over, new discussions may arise regarding LRTI pathogens. It is assumed that the samples used for the detection of pathogens will change drastically. In the reviewed studies, most of the samples to isolate LRTI agents were collected from sputum, TA, pleural effusion, and BAL. However, the lack of rapid, inexpensive, and easily applicable diagnostic methods and/or tools for these samples remains a critical challenge in this regard. Currently, gram-staining is considered to be the only effective option although its value remains controversial (55). Unfortunately, suggestions on rapid conventional and/or automated diagnostic tools were not proposed in the reviewed studies.

A notable finding on this systematic review was that studies regarding LRTI were more abundant during 2010-2020 within the past three decades, which could be attributed to several factors, such as the progress achieved in identification and antimicrobial susceptibility technologies of pathogens.

The main conclusions of the reviewed studies have been summarized below:

- LRTIs are two major causes of global mortality. In addition, hospital-acquired infections are the leading cause of mortality and morbidity in intensive care units (ICUs). The use of broad-spectrum antibiotics leads to the development of more resistant strains. With increased bacterial resistance, appropriate and effective antibiotic treatment may be delayed, which in turn leads to higher sepsis frequency and mortality rates (52).

- Evidently, the resistance rate of gram-negative microorganisms to various antibiotics has increased over the years due to the continuous or long-term use of antibiotics in hospitals. *P. aeruginosa* is a typical example in this regard, which remains an important pathogen in terms of nosocomial infections, especially in ICUs (52).

- No significant change has been reported in the short-term antimicrobial susceptibility of LRTI agents, and the antibiotics to be used in empirical treatments should be selected meticulously. Additionally, it is essential to evaluate the long-term effectiveness of empirical treatment approaches to plan for the necessary changes (38).

- It is essential to periodically determine the pathogens that cause LRTIs, as well as sensitivity to the antibiotics used in empirical treatment protocols (44).

5.1. Strengths and Limitations

To the best of our knowledge, this is the first study to compile the reports on bacterial LRTI agents. One of the limitations of this systematic review was that we could not review the studies providing data on fewer than 10 patients and did not discriminate between upper respiratory tract infections and LRTIs. In addition, errors are possible due to the differences in the identification methods and the experts who evaluate culture results. Therefore, the generalization of the results should be further discussed.

5.2. Conclusions

Since the disease course of bacterial LRTIs is generally mild, uncomplicated, and similar to non-bacterial LRTIs, physicians should not prescribe antibiotics to the patients without the detection of LRTI agents even if they are bacterial. This systematic review was focused on the reported data on the 30-year frequency of LRTI agents. As the frequency of LRTI bacterial factors is specific to each country, healthcare professionals may be able to report cultures and prescribe/select antibiotics. These findings could contribute to the prevention and reduction of antibiotic resistance, which is a major health issue today. It is recommended that further investigations be conducted on homogeneous samples to discuss the frequency of LRTI agents more generally. Furthermore, periodic evaluations could largely contribute to the current literature and treatment guidelines in this regard.

Footnotes

Authors' Contribution: I.H.C. conceived and designed the evaluation and drafted the manuscript. E. P. K. participated in designing the evaluation, performed parts of the statistical analysis and helped to draft the manuscript. I.K. re-evaluated the clinical data, revised the manuscript and performed the statistical analysis and revised the manuscript. I. K. collected the clinical data, interpreted them and revised the manuscript. I. H. C. re-analyzed the clinical and statistical data and revised the manuscript. All authors read and approved the final manuscript.

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