Aspiration in Head and Neck Cancer Patients: A Single Centre Experience of Clinical Profile, Bacterial Isolates and Antibiotic Sensitivity Pattern

K. C. Lakshmaiah · Nagesh T. Sirsath · Jayshree R. Subramanyam ·
Babu K. Govind · D. Lokanatha · Ashok M. Shenoy

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Abstract Most patients with head and neck cancer have dysphagia and are at increased risk of having aspiration and subsequent pneumonia. It can cause prolonged hospitalization, treatment delay and/or interruption and mortality in cancer patients. The treatment of these infections often relies on empirical antibiotics based on local microbiology and antibiotic sensitivity patterns. The aim of present study is to analyse respiratory tract pathogens isolated by sputum culture in head and neck cancer patients undergoing treatment at a tertiary cancer centre in South India who presented with features of aspiration. The study is carried out to establish empirical antibiotic policy for head and neck cancer patients who present with features of aspiration. This was a retrospective study. The study included sputum samples sent for culture and sensitivity from January 2011 to December 2012. Analysis of microbiologic species isolated in sputum specimen and the antibiotic sensitivity pattern of the bacterial isolates was performed. A detailed study of case files of all patients was done to find out which is the most common site prone for producing

aspiration. There were 47 (31.54 %) gram positive isolates and 102 (68.45 %) gram negative isolates. The most common bacterial isolates were *Klebsiella pneumoniae* (25.50 %), *Pseudomonas aeruginosa* (16.77 %) and *Haemophilus influenzae* (15.43 %). Levofloxacin was the most effective antibiotic with excellent activity against both gram positive and gram negative isolates. Most patients with aspiration had laryngeal cancer (34.89 %). Aspiration pneumonia was present in 14 (9.39 %) patients. Gram negative bacteria are common etiologic agents in head and neck cancer patients presenting with features of aspiration. Levofloxacin should be started as empirical antibiotic in these patients while awaiting sputum culture sensitivity report. As aspiration in head and neck cancer is an underreported event such institutional antibiotic sensitivity studies should be encouraged for prompt initiation of antibiotic that is most likely to be effective against etiologic pathogens.

Keywords Head and neck cancer · Sputum culture · Antibiotic sensitivity · Aspiration

K. C. Lakshmaiah · N. T. Sirsath (✉) · B. K. Govind ·
D. Lokanatha

Department of Medical Oncology, Kidwai Memorial Institute
of Oncology, Room No. 203, PG Hostel, M.H. Mari Gowda
Road, Bangalore 560029, Karnataka, India
e-mail: nagesh.sirsath@yahoo.com

J. R. Subramanyam

Department of Microbiology, Kidwai Memorial Institute
of Oncology, M.H. Mari Gowda Road, Bangalore 560029,
Karnataka, India

A. M. Shenoy

Department of Head and Neck Oncology, Kidwai Memorial
Institute of Oncology, M.H. Mari Gowda Road,
Bangalore 560029, Karnataka, India

Introduction

Patients with locally advanced head and neck cancer treated with chemotherapy or radiotherapy have a high risk of developing aspiration pneumonia. Poor oral intake either due to disease itself or radiation or chemotherapy induced oral mucositis; pre-treatment malnourished status and weakened immune system; chemotherapy induced neutropenia will all contribute to increased susceptibility to respiratory infections in this subset of patients. Swallowing problems often occur in patients with head and neck cancers. Patients who have trouble swallowing may aspirate when trying to eat or drink. If aspiration occurs during

treatment, its combination with neutropenia resulting from the chemotherapy may lead to aspiration pneumonia, sepsis and respiratory failure. The incidence of aspiration rate following chemoradiation for head and neck cancer is as high as 68 % [1]. All the patients with aspiration may not develop pneumonia. The reported incidence of aspiration pneumonia is around 14.54 % [2]. Aspiration is seen in all primary sites of head and neck cancer, sometimes it is seen more frequently in patients with cancer of the larynx and hypopharynx. It can cause prolonged hospitalization, treatment delay and/or interruption and mortality in cancer patients. The treatment of these infections often relies on empirical antibiotics based on local microbiology and antibiotic sensitivity patterns. The present study analyses respiratory tract pathogens isolated by sputum culture in head and neck cancer patients undergoing treatment at a tertiary cancer centre in South India. The study is carried out to establish empirical antibiotic policy for head and neck cancer patients who present with features of aspiration. An attempt was also made to find out which is the most vulnerable site in head and neck cancer prone for producing aspiration. Clinical profile of patients and ultimate outcome after episode of aspiration were analysed.

Materials and Methods

This was a retrospective study conducted at a tertiary care centre for cancer in South India. We analysed sputum culture reports of head and neck cancer patients who have been receiving chemotherapy or chemoradiation for locally advanced head and neck cancer and who presented with features of aspiration. The study included sputum samples sent for culture and sensitivity from January 2011 to December 2012. Analysis of microbiologic species isolated in sputum specimen and the antibiotic sensitivity pattern of the bacterial isolates was performed. A detailed study of case files of all patients was done to find out which is the most common site prone for producing aspiration. Clinical profile of patients and ultimate outcome after episode of aspiration were analysed.

Statistical Method

The isolates were mapped on WHONET 5.4 software and analysed using the same programme.

Results

A total of 149 isolates were cultured from sputum samples over a period of 2 years. There were 47 (31.54 %) gram positive isolates and 102 (68.45 %) gram negative isolates.

The most common bacterial isolates were *Klebsiella pneumoniae* (25.50 %), *Pseudomonas aeruginosa* (16.77 %) and *Haemophilus influenzae* (15.43 %). *Streptococcus pneumoniae* and *Staphylococcus aureus* accounted for 17 sputum isolates each (11.40 %). *Beta haemolytic streptococci* were isolated in 9 (6.04 %) sputum samples. *Acinetobacter baumannii* which is establishing itself as an emerging pathogen was isolated in 8 (5.36 %) sputum specimen and *Escherichia coli* also contributed the same (5.36 %). There were 4 (2.68 %) methicillin resistant *S. aureus* isolates. (Table 1 shows distribution of bacterial isolates from sputum specimen.)

There was a fair degree of resistance of gram negative isolates to third generation cephalosporins. A total of 76 isolates were tested for cefotaxime sensitivity out of which 12 (15.78 %) were resistant to cefotaxime. The resistant strains included 7 out of 38 (18.42 %) tested isolates of *K. pneumoniae*, 3 out of 8 (37.5 %) tested isolates of *A. baumannii* and 2 out of 8 (25 %) tested isolates of *E. coli*. Only 5 isolates of *H. influenzae* were subjected to cefotaxime sensitivity with all 5 being susceptible to it. *P. aeruginosa* isolates were not tested for cefotaxime susceptibility. The gram positive *S. pneumoniae* was highly susceptible to cefotaxime with all 17 isolates being sensitive to it. Cefixime also was found short of complete gram negative coverage with 10 out of tested 70 (14.29 %) gram negative isolates being resistant to cefixime. Of noteworthy, all 23 isolates of *H. influenzae* were sensitive to cefixime. Other isolates sensitive to cefixime included 26 out of tested 29 (89.65 %) isolates of *K. pneumoniae*, 6 out of tested 8 (75 %) isolates of *A. baumannii*, 3 out of tested 7 (42.85 %) isolates of *E. coli* and 2 out of tested 3 (66.6 %) isolates of *P. aeruginosa*. The antipseudomonal third generation cephalosporin ceftazidime showed better activity against gram negative isolates with 63 out of 69 (91.30 %) tested isolates being susceptible to it. 4 out of tested 32 (12.5 %) isolates of *K. pneumoniae* and 1 out of tested 8 (12.5 %) isolates of *E. coli* were resistant to it.

Table 1 Distribution of bacterial isolates from sputum samples

Organism	Number of isolates (total 149 isolates)
<i>Klebsiella pneumoniae</i>	38 (25.50 %)
<i>Pseudomonas aeruginosa</i>	25 (16.77 %)
<i>Haemophilus influenzae</i>	23 (15.43 %)
<i>Streptococcus pneumoniae</i>	17 (11.40 %)
<i>Staphylococcus aureus</i>	17 (11.40 %)
<i>Beta haemolytic streptococci</i>	09 (6.04 %)
<i>Acinetobacter baumannii</i>	08 (5.36 %)
<i>E. coli</i>	08 (5.36 %)
Methicillin resistant <i>S. aureus</i>	04 (2.68 %)

Table 2 Susceptibility of gram negative isolates to various tested antibiotics

Antibiotic	% Susceptibility				
	<i>Klebsiella pneumoniae</i> (%)	<i>Pseudomonas aeruginosa</i>	<i>Haemophilus influenzae</i>	<i>Acinetobacter baumannii</i> (%)	<i>E. coli</i>
CTX	81.57	–	–	62.5	75 %
CEFIX	89.65	66.6 %	100 %	75	42.85 %
CEFTA	87.5	96 %	–	87.5	100 %
CFS	100	100 %	–	100	100 %
PT	100	100 %	–	100	100 %
AK	100	85.72 %	–	75	100 %
CIPRO	71.42	76 %	–	25	–
LEVO	100	83.33 %	100 %	100	100 %
AC	70.58	–	100 %	66.6	50 %

CTX cefotaxime, CEFIX cefixime, CEFTA ceftazidime, CFS cefoperazone-sulbactam, PT piperacillin-tazobactam, AK amikacin, CIPRO ciprofloxacin, LEVO levofloxacin, AC amoxycillin-clavulanic acid

isolates of *A. baumannii* were resistant to ceftazidime. Out of the 25 isolates of *P. aeruginosa*, 24 (96 %) were sensitive to ceftazidime. All tested 4 isolates of *E. coli* were sensitive to ceftazidime.

Interestingly levofloxacin showed 100 % activity against 17 tested isolates of *K. pneumoniae*, 18 tested isolates of *H. influenzae*, 2 tested isolates of *A. baumannii* and *E. coli* each. Levofloxacin also showed good anti-pseudomonal activity with 20 out of 24 (83.33 %) tested isolates being sensitive to it. Cefoperazone-sulbactam was also 100 % effective antibiotic against all tested gram negative isolates. A total of 81 isolates were subjected to cefoperazone-sulbactam susceptibility with all 81 being sensitive to this antibiotic. *K. pneumoniae*, *P. aeruginosa*, *A. baumannii* and *E. coli* showed 100 % sensitivity to this antibiotic while 2 out of 17 (11.76 %) *S. aureus* were sensitive to cefoperazone-sulbactam. *H. influenzae* isolates were not tested for cefoperazone-sulbactam sensitivity. Piperacillin-tazobactam was also 100 % effective against tested gram negative isolates with all tested 34 isolates of *K. pneumoniae*, 21 isolates of *P. aeruginosa*, 8 isolates of *A. baumannii* and 6 isolates of *E. coli* showing piperacillin-tazobactam sensitivity. Few *S. aureus* (11.76 %) were also sensitive to piperacillin-tazobactam. Organisms not tested for piperacillin-tazobactam sensitivity were *H. influenzae*. Meropenem sensitivity was tested in 33 isolates with all being sensitive to it.

Amikacin also showed good antimicrobial activity against gram negative isolates with 52 out of tested 56 (92.86 %) gram negative sensitive to amikacin. 3 out of tested 21 (14.28 %) isolates of *P. aeruginosa* and 1 out of tested 4 isolates of *A. baumannii* (25 %) were resistant to amikacin while all tested isolates of *K. pneumoniae* and *E. coli* were sensitive to amikacin. Amikacin was also active against *S. aureus* with 14 out of 17 (82.35 %) *S. aureus* isolates sensitive to amikacin. Ciprofloxacin showed variable antimicrobial activity against gram negative isolates. *S. aureus* isolates also were sensitive to ciprofloxacin to some extent (41.17 %). (Table 2 shows susceptibility of gram negative isolates to various tested antibiotics.)

Amoxycillin-clavulanic acid showed an overall sensitivity of 73.91 % against all tested isolates with 51 out of 69 isolates being sensitive to it. 13 out of 16 (81.25 %) tested isolates of *S. pneumoniae*, 10 out of 14 tested isolates of *S. aureus* (71.42 %) and 6 out of 8 (75 %) tested isolates of *Beta haemolytic streptococci* showed susceptibility to amoxycillin-clavulanic acid. Amoxycillin-clavulanic acid also showed variable activity against gram negative isolates with 12 out of 17 (70.58 %) tested isolates of *K. pneumoniae*, 4 out of 6 (66.66 %) tested isolates of *A. baumannii*, 2 out of 4 (50 %) isolates of *E. coli* and all tested 4 isolates of *H. influenzae* being sensitive to it. Linezolid, teicoplanin and vancomycin were effective

Table 3 Susceptibility of gram positive isolates to various tested antibiotics

Antibiotic	% Susceptibility			
	<i>Streptococcus pneumoniae</i> (%)	<i>Staphylococcus aureus</i> (%)	<i>Beta haemolytic streptococci</i>	MRSA
AC	81.25	71.42	75 %	–
E	88.23	86.66	60 %	100 %
LZ	100	100	100	100 %
TEICO	100	100	100 %	100 %
VANCO	100	100	100 %	100 %
LEVO	86.66	100	100 %	100 %

AC amoxycillin-clavulanic acid, E erythromycin, LZ linezolid, TEICO teicoplanin, VANCO vancomycin, LEVO levofloxacin

against all gram positive isolates tested. In addition to excellent gram negative coverage, levofloxacin showed 100 % efficacy against tested isolates of *S. aureus* and *Beta haemolytic streptococci* and methicillin resistant *S. aureus* while 13 out of 15 (86.66 %) isolates of *S. pneumoniae* were sensitive to levofloxacin. All 4 isolates of methicillin resistant *S. aureus* were susceptible to levofloxacin, erythromycin, linezolid, teicoplanin and vancomycin. (Table 3 shows susceptibility of gram positive isolates to various tested antibiotics.)

A detailed analysis of case records of patients showed that majority of patients with positive sputum were having laryngeal cancer (34.89 %) followed by tongue cancer (22.14 %). 93 patients (62.41 %) had stage IV malignancy while 56 (37.58 %) patients had stage III disease. Aspiration was particularly common in patients who were being treated

with chemoradiation. Out of 149 sputum isolates, 103 (69.12 %) belonged to patients who were receiving weekly platinum along with radiotherapy. Majority of patients (52.34 %) developed features of aspiration 2–4 weeks after initiation of chemoradiation or chemotherapy. Most (94.63 %) patients had difficulty in swallowing. 122 (81.87 %) patients complained of cough with expectoration (81.87 %). Fever was associated with cough in only 13 (8.72 %) patients. Simultaneous blood culture was also sent in these patients along with sputum culture, however only 3 blood culture samples yielded growth which was the same as obtained by sputum culture. Chest X-ray was done in all these patients which was normal in most of the patients, while 14 (9.39 %) patients had consolidation radiologically (10 patients right upper lobe, 3 right middle lobe and 1 left lower lobe). Sputum culture showed that in these 14 patients, there

Table 4 Patient characteristics in present study

Gender	
Male	85 (57.04 %)
Female	64 (42.95 %)
Site of tumor	
Larynx	52 (34.89 %)
Tongue	33 (22.14 %)
Pyriiform sinus	19 (12.75 %)
Buccal mucosa	17 (11.40 %)
Post. pharyngeal wall	15 (10.06 %)
Tonsil	08 (5.36 %)
Oropharynx	05 (3.35 %)
Stage	
Stage III	56 (37.58 %)
Stage IV	93 (62.41 %)
Treatment received	
Chemotherapy	46 (30.87 %)
Chemoradiation	103 (69.12 %)
Symptom onset after initiation of CT/RT	
<2 weeks	57 (38.25 %)
2–4 weeks	78 (52.34 %)
>4 weeks	14 (9.39 %)
Clinical profile	
Cough with expectoration	122 (81.87 %)
Cough + fever	13 (8.72 %)
Dysphagia	141 (94.63 %)
Consolidation radiological/clinical	14 (9.39 %)
Absolute neutrophil count	
Normal	109 (73.15 %)
Neutropenia grade I/II	27 (18.12 %)
Neutropenia grade III/IV	13 (8.72 %)
Outcome	
Recovery but treatment delay	127 (85.23 %)
Treatment discontinuation	18 (12.08 %)
Death	4 (2.68 %)

were 7 *K. pneumoniae* isolates, 5 *P. aeruginosa* isolates and 2 acinetobacter isolates. These patients received combination of cefoperazone-sulbactam and levofloxacin. 10 patients recovered completely but unfortunately 4 patients did not improve even after addition of meropenem and died due to respiratory failure. All these 4 patients had grade IV neutropenia and were receiving weekly carboplatin along with radiotherapy. Except these 4 patients majority of patients recovered uneventfully. They received initial empirical doses of either amoxicillin-clavulanic acid or levofloxacin followed by change of antibiotics according to sputum culture report, but in these patients further chemotherapy or chemoradiation was delayed by 10–15 days. Treatment discontinuation was noted in 18 (12.08 %) patients mainly because of unwillingness on patient part to continue treatment. (Table 4 illustrates patient characteristics in present study.)

Discussion

Locally advanced head and neck cancer carries a poor prognosis because of the high rate of loco-regional recurrences [3]. The combination of chemotherapy and radiation may improve the local control and survival rate because of the additive or synergistic effect of chemoradiation [4]. However, the radiosensitization effect of chemotherapy may also lead to increased acute toxicity and late complications [5]. The radiation therapy fields usually cover a large area of head and neck to ensure that tumor bed and regional lymph nodes receive an adequate dose. Critical structures necessary for normal deglutition, such as tongue, larynx and pharyngeal muscles, may be treated to a high radiation dose. The increased radiation dose may lead to hyperactivation of transforming growth factor $\beta 1$, a peptide involved in collagen deposition and degradation [6]. Excessive fibrosis may be responsible for abnormal motility of the deglutition muscles and may lead to the aspiration, dysphagia and stenosis observed following head and neck chemoradiation [7]. Patients with head and neck cancer often have dysphagia. The destruction of normal tissues by head-and-neck malignancies, surgery, inflammation, and/or radiation-induced

fibrosis of the pharyngeal muscles are potential mechanisms responsible for dysphagia in head-and-neck cancer patients [8]. When aspiration occurs because of compromise of the swallowing reflex, pneumonia and respiratory failure may lead to death [1].

Aspiration is a multifactorial, anatomically defined event. Lack of adequate shunting of the food bolus around the larynx, pharyngeal stasis, poor hypopharyngeal transit, loss of supraglottic sensation and food clearing, and inadequate glottic sensation and closure all play a role, with the final 2 factors ultimately permitting food entry into the lower respiratory tract. Aspiration pneumonia in head and neck cancer is an underreported event. In Machtay et al. [9] study, patients had induction chemotherapy with carboplatin and paclitaxel followed by concurrent chemoradiation. Two of the 53 patients (4 %) died from respiratory failure during chemotherapy and radiation. Eisbruch et al. [1] performed videofluoroscopic swallow studies following treatment for advanced head and neck cancer patients who were being treated with concurrent gemcitabine and radiation. One to three months post therapy, 68 % of the patients showed evidence of aspiration which persisted for up to 1 year. Six patients developed aspiration pneumonia and two died. It was noteworthy that the aspiration was often unrecognized, dysphagia being the only complaint. The patients had suppressed cough reflex when they aspirated. Pauloski et al. [10] also corroborated the silent nature of the aspiration with videofluoroscopic swallow studies. Patients who complained of dysphagia during radiation treatment had larger residue and a higher rate of aspiration (22 %) during the swallowing study compared to the ones with no dysphagia (3 %). Wu et al. [11] also noticed that following radiation for nasopharyngeal tumors, 41 % of their patients who complained of dysphagia revealed silent aspiration during the endoscopic swallowing examination. In the study by Nguyen et al. [2] 55 patients with locally advanced head and neck cancer were treated with chemoradiation. 8 patients developed aspiration pneumonia and 5 died. Silent aspiration detected by modified barium swallow was present in 36 % patients. In present study 14 (9.39 %) patients had aspiration pneumonia out of which

Table 5 Aspiration rate following chemoradiation for locally advanced head and neck cancer

Authors	No. of patients	Chemotherapy	Radiation (Gy)	Aspiration rate (%)	Aspiration pneumonia rate (%)
Machtay et al. [9]	53	CP, P	70	4	4
Eisbruch et al. [1]	25	G	70	68	24
Pauloski et al. [10]	132	NS	NS	22	
Nguyen et al. [2].	55	NS	NS	36	14.54
Present study	149	5-FU+ Cs Cs + P Cs, CP	70		9.39

CP carboplatin, Cs cisplatin, P paclitaxel, 5-FU 5-fluorouracil, G gemcitabine, NS not-specified

4 died. (Table 5 illustrates aspiration rate following chemoradiation for locally advanced head and neck cancer).

In present study majority (34.89 %) of patients with aspiration had laryngeal cancer followed by tongue cancer (22.14 %). In contrast, Stenson et al. [12] reported that the incidence rate of aspiration reaches 30, 67, and 80 % in patients with oral, laryngeal, and pharyngeal head and neck cancers respectively, whereas Starmer et al. [13] reported that head and neck cancer involving the larynx or the hypopharynx is a principal risk factor for aspiration. Eischbruch et al. [1] reported that though swallowing-related structures were normal, radio therapy and chemotherapy affects movement of the oral cavity and laryngopharyngeal musculature and, thus, causes aspiration. Nguyen et al. [14], who conducted a study on patients with oropharyngeal cancer that underwent radiotherapy or chemotherapy, reported that the risk of aspiration was higher in patients with tumors classified as T3 or T4 than in those classified as T1 or T2. This result was consistent with results in our study as in present study 62.41 % patients with positive sputum culture had stage IV malignancy. The majority of patients who presented with features of aspiration were receiving chemoradiation (69.12 %). This finding agrees with the report of Nguyen et al. [15] that dysphagia and aspiration develop more often in patients who undergo both chemotherapy and radiotherapy than in those who undergo radiotherapy alone.

In present study majority of isolates were gram negative (68.45 %), the most common being *K. pneumoniae* (25.50 %) followed by *P. aeruginosa* (16.77 %) and *H. influenzae* (15.43 %). Kamath et al. [16] in their study of effect of irradiation on oropharyngeal bacterial and mycotic flora in head and neck cancer patients found out that *S. pneumoniae* and *Klebsiella* were the predominant isolates post irradiation, however they used throat swabs for analysis of bacterial isolates in their study. In present study there was a fair degree of resistance of gram negative sputum isolates to third generation cephalosporins, however not to the same extent as exhibited by gram negative blood stream isolates in the study of Prabhash et al. [17] as in their study of blood stream infections in cancer patients only 27.1 % gram negative isolates were sensitive to third generation cephalosporins. Levofloxacin was found to be the most effective antibiotic against most gram negative and gram positive sputum isolates in present study. We reached to the conclusion that levofloxacin should be started as empirical antibiotic in our hospital patients who present with features of aspiration while receiving chemotherapy or chemoradiation for advanced head and neck cancer while awaiting sputum culture sensitivity report. As aspiration in head and neck cancer is an underreported event such institutional antibiotic sensitivity studies should be encouraged for prompt initiation of antibiotic that is most likely to be effective against etiologic pathogens.

Conflict of interest None.

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