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Original Research

Prophylactic antibiotics reduce hospitalisations and cost in locally advanced head and neck cancer patients treated with chemoradiotherapy: A randomised phase 2 study

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Abstract ***Background:*** Platinum-based chemoradiotherapy for locally advanced head and neck cancer (LAHNC) induces a high rate of acute toxicity, including dysphagia and aspiration pneumonia. We hypothesised that prophylactic antibiotics can prevent pneumonia and hospitalisations and can be cost-effective.
Patient and methods: In this multicentre randomised trial, patients with LAHNC treated with chemoradiotherapy received prophylactic amoxicillin/clavulanic acid from day 29 after the start of treatment until 14 days after completion of chemoradiotherapy or standard care

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without prophylaxis. The primary objective was to observe a reduction in pneumonias. Secondary objectives were to evaluate the hospitalisation rate, adverse events, costs and health-related quality of life.

Results: One hundred six patients were included; of which, 95 were randomised: 48 patients were allocated to the standard group and 47 patients to the prophylaxis group. A pneumonia during chemoradiotherapy and follow-up until 3.5 months was observed in 22 (45.8%) of 48 patients in the standard group and in 22 (46.8%) of 47 patients in the prophylaxis group ($p = 0.54$). Hospitalisation rate was significantly higher in the standard group versus the prophylaxis group, 19 of 48 pts (39.6%) versus 9 of 47 pts (19.1%), respectively ($p = 0.03$). Significantly more episodes with fever of any grade were observed in the standard group (29.2% vs 10.2%, $p = 0.028$). A significant difference in costs was found, with an average reduction of €1425 per patient in favour of the prophylaxis group.

Conclusion: Although prophylactic antibiotics during chemoradiotherapy for patients with LAHNC did not reduce the incidence of pneumonias, it did reduce hospitalisation rates and episodes with fever significantly and consequently tended to be cost-effective.

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1. Introduction

Head and neck cancer affects almost 600 000 patients at a global level yearly. A substantial part of the patients has locally advanced disease at diagnosis. Concomitant platinum-based chemoradiotherapy is the treatment of choice for locally advanced head and neck carcinoma (LAHNC) and can be applied as primary or as postoperative treatment [1]. However, chemoradiotherapy induces a high rate of acute toxicities such as mucositis and dysphagia.

Dysphagia can lead to aspiration, which is defined as passage of material below the level of the vocal cords [2]. Dysphagia and aspiration during and after chemoradiotherapy for head and neck cancer are usually underreported [3–5]. In patients with LAHNC, the incidence of aspiration at diagnosis ranges from 9 to 53% [3,6] and the aspiration rate during and after chemoradiotherapy is between 13 and 69% [5–7]. Aspiration pneumonia, defined as pneumonia secondary to inhalation of food particles, saliva or other foreign substances [4], often leads to (prolonged) hospitalisation and is a major cause of morbidity and mortality [8]. Xu *et al.* [4] demonstrated a 5-year cumulative incidence of aspiration pneumonia in head and neck cancer patients of 23.8%, with a hospital admission rate of 84% and 47% requiring an admission to an intensive care. The mortality rate after aspiration pneumonia varies between studies from 17% to 32.5% [4,9]. Because of this high incidence of aspiration pneumonia in patients with LAHNC treated with chemoradiotherapy, we hypothesised that prophylactic antibiotics could lower the number of pneumonias and hospitalisations. To our knowledge, this is the first prospective study that investigates the effect of prophylactic antibiotics in patients with LAHNC treated with chemoradiotherapy. The primary aim of this multicentre randomised study was to investigate the efficacy of prophylactic antibiotics versus standard treatment to prevent aspiration pneumonia during chemoradiotherapy in patients with LAHNC. Secondary aims were to investigate the effect on the number of hospitalisations and cost-effectiveness and to evaluate the adverse events and health-related quality of life (HRQoL).

2. Methods

2.1. Patients and study design

Patients with LAHNC who were treated with chemoradiotherapy, as primary or as postoperative treatment, were eligible. Participating patients were included and registered before the start of chemoradiotherapy. Exclusion criteria for registration included an allergy to amoxicillin, the use of maintenance antibiotics or immunodeficiency. Patients were randomised between day 21 and 28 after the start of treatment if there were no additional exclusion criteria including pneumonia, other infections or use of antibiotic treatment within the last 2 weeks before randomisation. Patients were allocated equally to the two treatment groups by minimisation, which is a method of adaptive stratification allowing higher numbers of stratification factors, for smoking, chronic obstructive pulmonary disease (Global initiative for chronic obstructive lung disease (GOLD) 0–2 or GOLD 3–4), weight loss (more than 10% versus less than 10%), primary site of the tumour (oral cavity, oropharyngeal or hypopharyngeal and laryngeal cancer), participating centre and human papillomavirus positivity [10].

The trial was approved by the Medical Ethical Research Committee, in accordance with the Declaration of Helsinki, and registered at *clinicaltrials.gov* (*NCT01598402*). All patients signed written informed consent.

Laboratory and adverse events, scored by the Common Terminology Criteria for Adverse Events, version 4.0, were registered every week during chemoradiotherapy and one week, three weeks and 3.5 months after completing chemoradiotherapy. Sputum cultures were obtained on day 29 and at 1 week, 3 weeks and 3.5 months after chemoradiotherapy. HRQoL questionnaires, among which was the EuroQol-5D (EQ-5D), were collected at baseline, day 28 (one day before starting prophylactic antibiotics), the last day of radiotherapy and 3.5 months after the end of chemoradiotherapy. For the EQ-5D, utilities were calculated, resulting in a score between zero and one. A score of one means perfect health, whereas zero means death [11].

The primary end-point was to evaluate the number of definite or suspected pneumonias. A definite pneumonia was defined as an infiltrate on chest radiography or the presence of 3 or more of the following 4 features: sustained fever (temperature >38.0 °C), rales or rhonchi on chest auscultation, sputum Gram stain showing substantial leukocytes (i.e. more than 5 leucocytes per high-power field, ×100) or sputum culture growing a respiratory pathogen. A suspected pneumonia was defined as 2 of the 4 features [12].

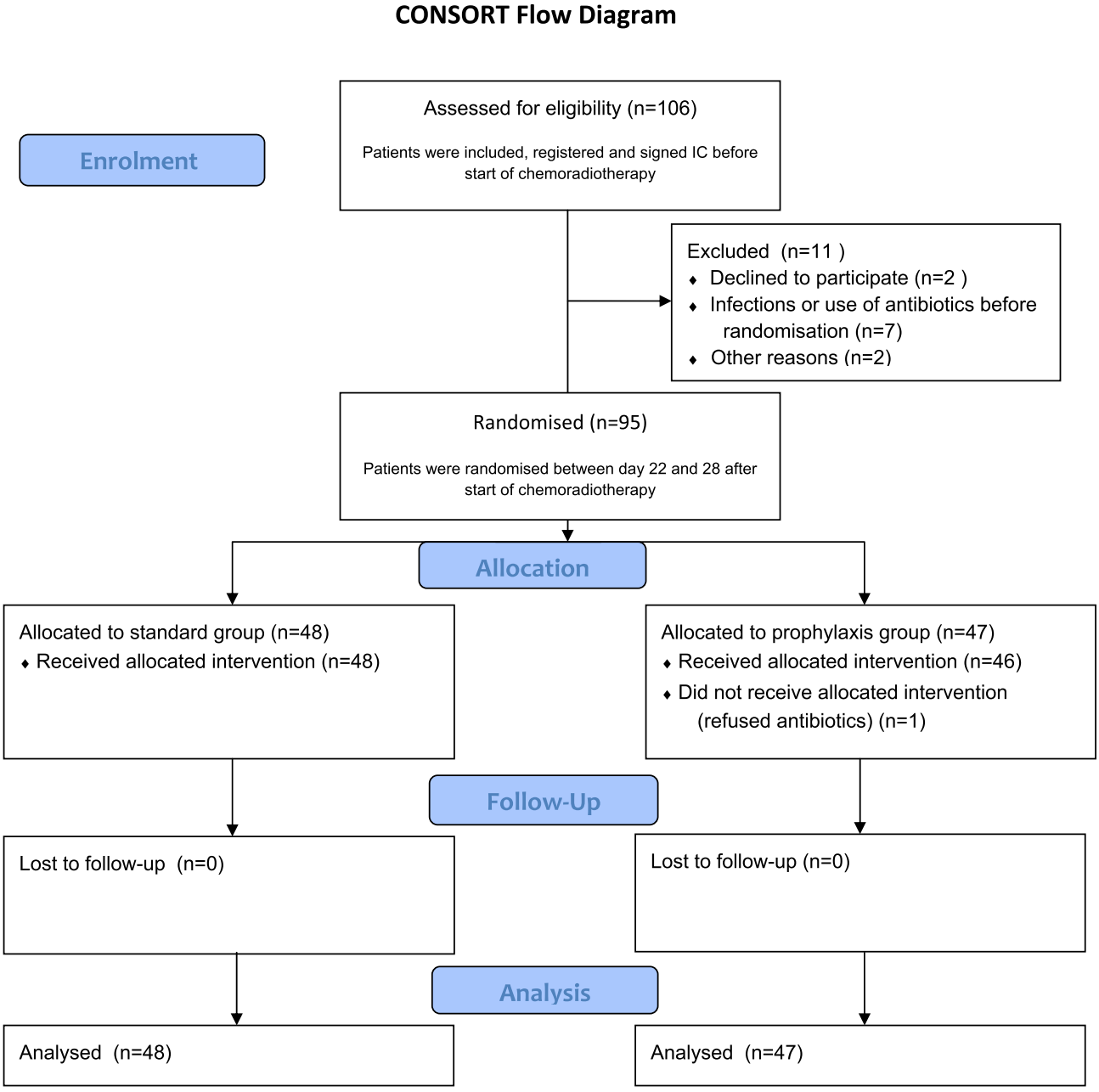

Fig. 1. Patient selection. IC, informed consent.

Secondary end-points were the number and duration of hospitalisations, toxicity, HRQoL and adverse events, cost-effectiveness and all-cause mortality.

2.2. Prophylactic antibiotics

The prophylaxis group received amoxicillin/clavulanic acid, oral suspension 625 mg three times a day (tid), from day 29 after the start of chemoradiotherapy until 14 days after completion, in addition to standard care. The standard group received no prophylactic antibiotics. In case of a (suspected) lower airway infection, blood and sputum cultures were taken and chest radiography was performed, mostly followed by hospitalisation and intravenous antibiotics.

2.3. Chemoradiotherapy

Chemotherapy consisted of cisplatin, given at a dose of 100 mg/m^2 every 3 weeks for 3 cycles or 40–50 mg/m^2 weekly for 6 or 7 cycles. Radiotherapy was given as per local practice with intensity-modulated radiation therapy and an accelerated (68Gy in 34 fractions of 2Gy in 5.5 weeks) or conventional scheme (70Gy in 35 fractions of 2Gy in 7 weeks) [13,1]. If a postoperative patient was not eligible for cisplatin, carboplatin was given weekly.

2.4. Statistical analysis

Under the assumption that the percentage of definite and/or suspected pneumonia in the standard group was 50% [6] and in the intervention group was 25% (a reduction of 50% [14]), 46 patients in each group were needed to have a power of 80% to detect a lower percentage in the prophylaxis group based on a one-sided binomial test at 5% significance level. A 15% adjustment for data attrition resulted in a sample size of 53 patients in each group. No power analysis was performed for the secondary end-points. Efficacy analysis was conducted in the intention-to-treat population, that is, all randomised patients. Non-parametric tests were performed using the one-sided Fisher exact test to test for significant decrease in pneumonias in the prophylaxis group, the chi-squared test for differences in hospitalisation and adverse events and Mann–Whitney tests for differences in costs. For the analysis of the EQ-5D questionnaire, an independent t-test was used.

2.5. Economic evaluation

An economic evaluation was performed alongside the clinical trial and was based on the general principle of a cost-effectiveness analysis. On patient level, volumes of care were measured prospectively. Per group, full cost prices were determined using activity-based costing. The Dutch guidelines for cost analyses were used [15]. The effects were measured using the earlier described EQ-5D HRQoL questionnaire.

Only three groups of medication were analysed: analgetics, antiemetics and proton pump inhibitors. The costs of the prophylactic treatment in the prophylaxis group were determined for amoxicillin/clavulanic acid suspension used for 4 weeks, with a total price of €20.16 per patient.

Table 1
Patient characteristics.

Patient characteristics	Standard group (N = 48)	Prophylaxis group (N = 47)
Age, yr (range)	58.5 (43–68)	57.0 (23–68)
Sex, no. (%)		
Female	14 (29.2)	11 (23.4)
Male	34 (70.8)	36 (76.6)
WHO (%)		
0	35 (72.9)	32 (68.1)
1	11 (22.9)	11 (23.4)
Unknown	2 (4.2)	4 (8.5)
Tumour site (%)		
Oral cavity	14 (29.2)	13 (27.7)
Oropharynx	20 (41.7)	20 (42.6)
Hypopharynx	5 (10.4)	11 (23.4)
Larynx	8 (16.7)	3 (6.4)
Unknown primary	1 (2.1)	0
TNM		
T		
1	5 (10.4)	4 (8.5)
2	9 (18.8)	10 (21.3)
3	15 (31.3)	13 (27.7)
4	18 (37.5)	19 (40.4)
x	1 (2.1)	1 (2.1)
N		
0	15 (31.3)	12 (25.5)
1	5 (10.4)	7 (14.9)
2a	4 (8.3)	3 (6.4)
2b	16 (33.3)	13 (27.7)
2c	7 (14.6)	10 921.3)
3	1 (2.1)	1 (2.1)
x	0	1 (2.1)
M		
0	46 (95.8)	45 (95.7)
x	2 (4.2)	2 (4.3)
Indication CRT (%)		
Primary treatment	26 (54.2)	34 (72.3)
Postoperative treatment	22 (45.8)	13 (27.7)
Chemotherapy administered (%)		
Cisplatin 100 mg/m2 thrice weekly	10 (20.8)	12 (25.5)
Cisplatin 40–50 mg/m2 weekly	32 (66.7)	30 (63.8)
Carboplatin AUC 1.5 weekly	2 (4.2)	1 (2.1)
Adapted chemotherapy	4 (8.3)	4 (8.4)
Radiotherapy administered (%)		
Conventional	22 (45.8)	21 (44.7)
Accelerated	26 (54.2)	26 (55.3)
Total dose given at primary tumour and pathological lymph nodes (median, range)	68.0 (60–70)	68.0 (60–70)
Total dose given at elective neck levels (median, range)	50.3 (46–66)	50.3 (46–60)
Tube feeding at randomisation (%)		
No	39 (81.3)	38 (80.9)
Yes	9 (18.8)	9 (19.1)

TNM, tumour-node-metastasis.

Table 2
Efficacy outcomes on definite and suspected pneumonias, number and duration of hospitalisation and costs.

Efficacy outcomes	Standard group ($N = 48$)	Prophylaxis group ($N = 47$)	p
Incidence of pneumonia	22 (45.8)	22 (46.8)	0.544
Type of pneumonia			
Definite	8 (16.7)	4 (8.5)	0.232
Suspected (%)	14 (29.2)	18 (38.3)	0.346
Hospitalised patients	19 (39.6)	9 (19.1)	**0.030**
Total days of hospitalisation			0.96
Median (range)	5.0 (2–41)	5.0 (1–9)	
Costs			
Hospitalisation			**0.032**
Mean per patient	€2076.48	€682.17	
Whole group	€99671.00	€32062.00	
Pain medication			0.382
Mean per patient	€78.34	€46.13	
Whole group	€3760.22	€2167.94	
Antiemetics			0.388
Mean per patient	€306.17	€288.15	
Whole group	€14696.31	€13543.16	
Proton pump inhibitors			0.597
Mean per patient	€0.81	€0.65	
Whole group	€39.27	€30.58	
Prophylactic antibiotics			0.00
Mean per patient	€0.00	€20.16	
Whole group	€0.00	€947.52	
Total costs			**0.046**
Mean per patient	€2461.80	€1037.26	
Whole group	€118166.79	€48751.20	

$p<0.05$:significantly different.

Table 3
Reasons for hospitalisation in both treatment groups.

Reason for hospitalisation	Standard group (19/48 patients hospitalised)	Prophylaxis group (9/47 patients hospitalised)
Pneumonia	1	2
Fever	5	1
Candida mucositis		1
Nausea and vomiting	2	
Dehydration	7	4
Pain	1	
Dysphagia		1
Dyspnoea	2	
Hypercalcemia	1	
Fatigue		1
Other	2	

In the standard group, two patients had a combination of 2 reasons for hospitalisation, and in the prophylaxis group, one patient had a combination of 2 reasons for hospitalisation.

3. Results

3.1. Patient characteristics

Between January 2012 and July 2015, a total of 106 patients were included in 6 centres. At randomisation, 95 patients were randomised; 48 patients were allocated to the standard group and 47 patients to the prophylaxis group. Eleven patients could not be randomised (Fig. 1).

One patient in the prophylaxis group refused further participation after randomisation and was included into the intention-to-treat analysis for the primary objective as well as the cost-effectiveness, but no further information for secondary objectives was available for this patient.

The standard group and the prophylaxis group were well balanced in terms of baseline characteristics (Table 1). The median age of patients was 58.5 years in the standard group and 57.0 years in the prophylaxis group.

3.2. Treatment

3.2.1. Prophylactic antibiotics

In the prophylaxis group, 29 patients (61.7%) completed the amoxicillin/clavulanic acid prophylaxis as planned, that is, 625 mg tid from day 29 after the start of chemoradiotherapy until 14 days after completion. Reasons for early discontinuation in the other 18 patients were toxicity in 9 patients, mainly due to gastrointestinal complaints, refusal of antibiotics in 3 patients, non-compliance to the prescribed schedule in 4 patients and switch to alternative antibiotic treatment due to hospitalisation or febrile neutropenia during the course of prophylaxis in 2 patients.

3.2.2. Chemoradiotherapy

The chemoradiotherapy was delivered as stated in Table 1. In 4 patients of each treatment group, the chemotherapy was adapted because of toxicity

Table 4
Reported adverse events by the local investigator.

	Standard group ($N = 48$)		Prophylaxis group ($N = 46$)		p
CTCAE 4.0	Any grade	Grade 3-4	Any grade	Grade 3-4	
Allergic reaction	1 (2.1)	0 (0)	1 (2.2)	0 (0)	
Fatigue	40 (83.3)	1 (2.1)	31 (67.4)	1 (2.2)	
Fever	14 (29.2)	1 (2.1)	5 (10.9)	0 (0)	0.028
Weight loss	41 (85.4)	1 (2.1)	36 (78.3)	3 (6.5)	
Rash/desquamation	16 (33.3)	1 (2.1)	13 (28.3)	2 (4.3)	
Dermatitis radiation	33 (68.8)	4 (8.3)	31 (67.4)	9 (19.6)	
Anorexia	28 (58.3)	17 (35.4)	23 (50.0)	5 (10.9)	
Constipation	22 (45.8)	0 (0)	19 (41.3)	0 (0)	
Diarrhoea	11 (22.9)	2 (4.2)	9 (19.6)	0 (0)	
Oral mucositis	41 (85.4)	20 (41.7)	33 (71.7)	15 (32.6)	
Nausea	25 (52.1)	2 (4.2)	25 (54.3)	0 (0)	
Vomiting	20 (41.7)	3 (6.3)	14 (30.4)	0 (0)	
Dry mouth	33 (68.8)	0 (0)	32 (69.6)	0 (0)	
Dysphagia	40 (83.3)	21 (43.8)	33 (71.7)	13 (28.3)	
Foetor ex ore	2 (4.2)	0 (0)	2 (4.3)	0 (0)	
Cough	15 (31.3)	0 (0)	13 (28.3)	0 (0)	
Dyspnoea	8 (16.7)	0 (0)	3 (6.5)	1 (2.2)	
Pneumonitis	1 (2.1)	0 (0)	1 (2.2)	1 (2.2)	
Creatinine increased	35 (72.9)	2 (4.2)	30 (65.2)	0 (0)	
Tumour pain	7 (14.6)	0 (0)	14 (30.4)	0 (0)	
Pain head/neck	24 (50.0)	2 (4.2)	20 (43.5)	1 (2.2)	

CTCAE, Common Terminology Criteria for Adverse Events.

according to the treating physician. One patient in the standard group had a delay in radiotherapy during treatment, and one patient stopped prematurely. In the prophylaxis group, only one patient needed a delay in radiotherapy while on treatment.

3.3. Efficacy of prophylactic antibiotics

3.3.1. Pneumonia

No decrease was found in the incidence of (definite or suspected) pneumonia in the standard group compared with the prophylaxis group, 45.8% versus 46.8%, respectively ($p = 0.54$). In the standard group, 8 patients developed a definite pneumonia compared with 4 patients in the prophylaxis group (Table 2). There was no difference in the use of proton pump inhibitors between the two groups (39.6% versus 34.0% in the standard group and prophylaxis group, respectively, $p = 0.576$).

3.3.2. Hospitalisation

The hospitalisation rate was significantly different between both groups; in the standard group, 19 patients (39.6%) were hospitalised versus 9 (19.1%) in the prophylaxis group ($p = 0.03$). The median duration of hospitalisation was 5.0 days in both groups ($p = 0.96$) (Table 2). The main reasons for hospitalisations in both groups were related to the chemoradiotherapy and were frequently multifactorial determined by a combination of, for example, pneumonia, dehydration, fever, pain, mucositis or dyspnoea (Table 3).

3.3.3. Toxicity

A significant difference in episodes of fever (higher than 38.0 °C) was found between the standard group and the prophylaxis group (29.2% versus 10.9%, respectively, $p = 0.028$), with no difference in the frequency of neutropenia. With respect to other adverse events, no significant differences were found between both groups (Table 4).

3.3.4. Mortality

One patient, who was included but not randomised because of antibiotic use 14 days before randomisation, died during the 3.5-month follow-up due to progressive disease. All other patients were alive at the end of follow-up.

3.4. Economic evaluation and quality of life

The difference in costs of hospitalisation plus the medication used was significant between the standard group and the prophylaxis group, in favour of the prophylaxis group ($p = 0.046$), with a mean difference of €1425 per patient (Table 2). The EQ-5D HRQoL showed no significant differences. Because no differences were found between the two groups regarding the number of pneumonias and HRQoL measured by the EQ-5D, the cost-effectiveness decision rule became 'cost-minimisation', meaning that the treatment with the lowest costs is to be preferred. Following that rule, the prophylaxis group turned out to be cost-effective.

The full report on HRQoL of this study will be published separately.

3.5. Sputum cultures

During the entire study period, there was no significant difference in the number of patients with positive sputum cultures between the standard group and the prophylaxis group (29 patients [60.4%] in the standard group and 32 [68.1%] in the prophylaxis group, $p = 0.441$). Before the start of prophylactic antibiotics (day 29), after the end of chemoradiotherapy and 3 weeks after the end of chemoradiotherapy, no significant differences were found in the number of performed cultures, in the number of positive cultures for bacteria and/or fungi or in the number of cultures with resistant bacteria. At the end of follow-up, 3.5 months after the end of chemoradiotherapy, more positive cultures were found significantly in the prophylaxis group, although more resistant bacteria were cultured significantly in the standard group. However, only few sputum cultures were performed in both groups, probably because patients did not have any complaints anymore (Table 5).

4. Discussion

In this prospective randomised controlled trial investigating the role of antibiotic prophylaxis in patients with LAHNC treated with chemoradiotherapy, no decrease in the incidence of pneumonia in the group treated with prophylactic antibiotics versus standard care was found but there was a significant reduction in hospitalisation rate, episodes with fever and costs.

A reduction in episodes of fever as well as a reduction in hospitalisations is important, first, not only for the patients who already undergo an intensive treatment but also for the oncology services as patients with LAHNC treated with chemoradiotherapy are referred relatively often to acute and emergency departments where these unplanned admissions are an extra burden. In this patient population, different attempts have been made in the past to reduce acute admissions, such as an intensive nurse-led intervention or the use of percutaneous endoscopic gastrostomies to prevent aspiration pneumonias [16,17]. To the best of our knowledge, the use of antibiotic prophylaxis has not been investigated before in a randomised way in this patient population and the positive effect on the incidence of fever and hospitalisation is a novel and relevant result. Despite the fact that the difference in hospitalisation rate was not totally well understood, prophylactic antibiotics seem to improve general well-being with effect on multiple aspects, such as fever, mucositis, pain and dyspnoea.

There may be different reasons why the primary end-point of the study, a significant reduction in the

Table 5
Number of sputum cultures performed and the percentage of cultures positive for bacteria with resistant bacteria.

Sputum cultures	Day 29			After the end of CRT			3 weeks after CRT			3.5 months after CRT		
	Standard group (N = 48)	Prophylaxis group (N = 47)	p-value	Standard group (N = 48)	Prophylaxis group (N = 47)	p-value	Standard group (N = 48)	Prophylaxis group (N = 47)	p-value	Standard group (N = 48)	Prophylaxis group (N = 47)	p-value
Performed (%)	34 (70.8)	31 (66.0)	0.609	37 (77.1)	29 (61.7)	0.104	37 (77.1)	35 (74.5)	0.766	15 (31.2)	12 (25.5)	0.537
Negative (%)	23 (67.6)	15 (48.4)	0.116	20 (54.1)	9 (31.0)	0.061	18 (48.6)	15 (42.9)	0.622	8 (53.3)	1 (8.3)	0.014
Positive (%)	11 (32.4)	16 (51.6)		17 (45.9)	20 (69.0)		19 (51.4)	20 (57.1)		7 (46.7)	11 (91.7)	
Percentage of positive cultures with resistant bacteria (%)	14.3	40.0	0.252	38.5	61.5	0.239	27.3	42.9	0.420	83.3	20.0	0.036

incidence of pneumonias, was not reached. First, the hypothesis that prophylactic antibiotics could lower the number of pneumonias in patients with LAHNC by 50% was possibly overestimated. This estimation was based on a Cochrane review on prophylactic antibiotics in adult intensive care unit patients who showed a significant reduction of 50% in respiratory tract infections and mortality in adult patients, half of which received mechanical ventilation support. Second, in the prophylaxis group, only 61.7% completed the amoxicillin/clavulanic acid prophylaxis as planned, predominantly caused by poor compliance, which is partly due to this specific patient population. Whether this has influenced a lack of difference in incidence of pneumonias is unclear as it did not prevent the prophylaxis group from having a lower rate of episodes with fever. Third, non-significantly, more patients in the prophylaxis group received chemoradiotherapy as primary treatment, whereas, in the standard group, relatively more patients received chemoradiotherapy as postoperative treatment. However, in both groups, aspiration can occur. Finally, other risk factors, such as alcohol consumption, poor oral hygiene and use of sleeping pills, for aspiration pneumonia were not used as stratification factors and could have been confounders in this study [18].

There was a positive outcome for the secondary endpoint cost. Antibiotic prophylaxis intervention was cost-effective, with an average cost-saving of €1425 per patient. For the Netherlands, with an estimation of 300 patients with LAHNC treated with chemoradiotherapy each year, this could lead to a reduction of about €425,000 per year. To prevent the emergence of bacterial resistance, prudent use of antibiotics, particularly broad-spectrum agents such as amoxicillin/clavulanic acid, is warranted [19]. Although we did not observe any increase in bacterial resistance due to the use of prophylactic antibiotics, we realise that the study included a low number of patients to look for this end-point. Although the number of positive sputum cultures 3.5 months after the end of chemoradiotherapy was significantly higher in the prophylaxis group, the absolute number of cultures was too low to draw any meaningful conclusions. In addition, the long-term (>1 year) effects on resistance and related costs are unknown.

In conclusion, this randomised study suggests that the use of prophylactic antibiotics by patients with LAHNC during chemoradiotherapy does not reduce the number of pneumonias but does reduce the number of patients with fever and hospitalisations and costs and can, therefore, be considered in this population.

Conflict of interest statement

None declared.

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