

Adherence to antibiotic guidelines in the treatment of acute pharyngeal infections

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ABSTRACT

MINTRDUCTION: We aimed to investigate doctors' adherence to the local antibiotic guidelines for treatment of patients admitted with acute pharyngeal infections and to identify patient-related risk factors for non-adherence.

METHODS: All patients with acute tonsillitis, peritonsillar abscess (PTA), and parapharyngeal abscess admitted to the Ear-Nose-Throat Department, Aarhus University Hospital, in the 2001-2014 period were included in the study.

RESULTS: In total, 2,567 patients were hospitalised with acute pharyngeal infection. In non-allergic patients, penicillin was prescribed to 81%, either alone (48%) or in combination with metronidazole (33%). Macrolides (54%) and cefuroxime (44%) were the drugs of choice in 85 (98%) patients who were allergic to penicillin. Patients were prescribed antibiotics according to guidelines in 63% of cases. The addition of metronidazole to penicillin was the main (75% of cases) reason for non-adherence. Increasing patient age and male gender were independent risk factors for non-adherence. PTA patients treated according to the guidelines had a significantly shorter hospital stay than patients treated with additional metronidazole or broad-spectrum antibiotics.

CONCLUSIONS: A significant (37%) proportion of patients with acute pharyngeal infections were treated non-adherently to antibiotic guidelines, mainly because of (inappropriate) addition of metronidazole to penicillin.

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TRIAL REGISTRATION: The study was approved by the Danish Data Protection Agency.

Acute pharyngeal infections constitute common reasons for admission to ear, nose and throat (ENT) departments and intravenous antibiotic therapy [1]. Unnecessary prescribing of antibiotics in general and the increasing use of broad-spectrum antibiotics in particular are major drivers of resistance development, which is a major threat to modern healthcare [2]. Previous studies find that implementation of antibiotic guidelines reduce inappropriate antibiotic prescriptions [3] and the development of national antibiotic guidelines is encouraged [4]. At our department, doctors are recommended to follow the local antibiotic guidelines un-

less they find reason to deviate from standard treatment. While several studies of antibiotic guideline adherence have been conducted in primary care settings [5-9], we were unable to find antibiotic adherence studies conducted at ENT departments.

Thus, the aim of the current study was to evaluate adherence to local antibiotic guidelines for the treatment of patients admitted with acute pharyngeal infections. In addition, we aimed to identify patient-related risk factors for non-adherence and duration of hospitalisation.

METHODS

All patients admitted to our department in the 2001-2014 period with acute tonsillitis (AT), peritonsillar abscess (PTA), and/or parapharyngeal abscess (PPA) were included in the study. A clinical diagnosis of AT was based on symptoms and signs of tonsillar mucosa inflammation with or without peritonsillar phlegmon. A clinical diagnosis of PTA was based on visual detection of pus between the tonsillar capsule and the pharyngeal constrictor muscle. A clinical diagnosis of PPA was based on signs of deep neck infection with visual detection of pus peripherally to the pharyngeal constrictor muscle. Patients with concomitant PTA and PPA were categorised in the PPA group. PTA was surgically treated with either incision and drainage or acute tonsillectomy at the discretion of the physician in charge and the patient's preferences. All patients with PPA underwent surgical management (previously described [10]), most frequently including acute tonsillectomy and internal incision.

The antibiotic management of each patient was categorised as either in accordance with the current local guideline (adherence) or different from the guideline (non-adherence). Suspected antibiotic allergies were taken into account as well as described (in the medical charts) reasons for alternative antibiotic prescriptions. During the time period 2001-2014, two different guidelines were in force (changed 1 October 2011, **Table 1**). In patients who were allergic to penicillin, both guidelines instructed doctors to substitute penicillin with cefuroxime (except in case of prior anaphylaxis following penicillin administration).

The study was approved by the Danish Data Pro-

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 **TABLE 1**

Antibiotic guidelines for pharyngeal infections at the Department of Otorhinolaryngology, Head and Neck Surgery, Aarhus University Hospital, Denmark, before and after 1 October 2011, respectively. In patients with penicillin allergy, cefuroxime was recommended instead of penicillin.

	Before	After
Acute tonsillitis	Penicillin	Penicillin
<i>Peritonsillar abscess</i>		
Incision and drainage	Penicillin + metronidazole	Penicillin
Acute tonsillectomy	Penicillin or no antibiotic treatment	Penicillin or no antibiotic treatment
Parapharyngeal abscess	Penicillin + metronidazole	Penicillin + metronidazole

 **TABLE 2**

Choice of antibiotic treatment in 2,479 patients without known or suspected antibiotic allergies who were admitted with pharyngeal infection in the 2001-2014 period. The values are n (%).

	Adherence	Non-adherence	
		described reason	no described reason
<i>Acute tonsillitis (n = 759)</i>			
Penicillin:			
Penicillin + metronidazole			274
Cefuroxime			9
Cefuroxime + metronidazole			13
Ampicillin			15
Ampicillin + metronidazole			1
Subtotal	447 (59)	0	312 (41)
<i>Peritonsillar abscess (n = 1,631)</i>			
Tonsillectomy (n = 1,435):			
Penicillin	620		
Penicillin + metronidazole			396
No antibiotic	404		
Cefuroxime			5
Cefuroxime + metronidazole			5
Ampicillin			1
Other ^a			4
Incision & drainage (n = 185):			
Penicillin	27		84
Penicillin + metronidazole	51		21
Cefuroxime + metronidazole			2
No surgical intervention (n = 11):			
Penicillin	2		3
Penicillin + metronidazole	3		3
Subtotal (n = 1,631)	1,107 (68)	0	524 (32)
<i>Parapharyngeal abscess (n = 89)</i>			
Penicillin			19
Penicillin + metronidazole	54		
Cefuroxime			2
Cefuroxime + metronidazole			10
Ampicillin + metronidazole		3	
Piperacillin-tazobactam + metronidazole		1	
Subtotal	54 (65 ^b)	4	31 (35)
Total (N = 2,479)	1,612 ^b (65 ^b)		867 (35)

a) Metronidazole (n = 2), penicillin + ciprofloxacin (n = 1), ciprofloxacin + metronidazole (n = 1).

b) Including non-adherence, described reason.

tection Agency. In accordance with Danish law, the study was not reported to the local ethical committee.

Fisher's exact test was used to compare categorical variables. Student's t-test was used to compare continuous variables (univariate risk factor analysis), and multivariate logistic regression analysis was used on statistically significant risk factors in univariate analysis. The normality of the data was assessed using quantile-quantile plots. The level of significance was set to $p < 0.05$.

Trial registration: The study was approved by the Danish Data Protection Agency.

RESULTS

Population

During the 14-year study period, a total of 2,567 patients were admitted to our department with AT (n = 793), PTA (n = 1,681) or PPA (n = 93). Allergy to penicillin was known or suspected in 88 (3.4%) patients. No patients were allergic to other antibiotics.

Choice of antibiotic therapy in non-allergic patients

In all 81% (2,005/2,479) of the patients without known or suspected antibiotic allergies were prescribed penicillin, either alone (n = 1,202) or in combination with metronidazole (n = 802) or ciprofloxacin (n = 1) (Table 2). A total of 404 (16%) patients undergoing acute quinsy tonsillectomy were not treated with antibiotics. Cefuroxime was given to 46 (1.8%) patients. Other antibiotics were prescribed to 24 (1.0%) patients.

In patients with AT, penicillin was the drug of choice in 95% of cases, either alone (n = 447) or in combination with metronidazole (n = 274) (Table 2). The remaining 38 (5.0%) patients were treated with more broad-spectrum antibiotics.

Patients with PTA (Figure 1) underwent either acute tonsillectomy (n = 1,435) or incision and drainage (n = 185). In addition, eleven patients had no surgical intervention (two patients refused surgery and nine patients had spontaneous perforation). In patients undergoing acute tonsillectomy, 1,016 (71%) patients were treated with penicillin (in combination with metronidazole in 396 of the cases), no antibiotics were given to 404 (28%) patients, and 15 (1.0%) patients were prescribed more broad-spectrum antibiotics. 99% of PTA patients undergoing incision and drainage were treated with penicillin, either as monotherapy (n = 111) or in combination with metronidazole (n = 72).

Penicillin was the drug of choice in 82% (73/89) of patients with PPA, either as monotherapy (n = 19) or in combination with metronidazole (n = 54). Contrary to the two other groups of patients, reasons for deviating from the guideline were described in the records of

four (4.5%) patients with PPA: penicillin was substituted with ampicillin (because the primary site of infection was the epiglottis, $n = 3$) or piperacillin-tazobactam (in a patient with Lemierre's syndrome).

Choice of antibiotic therapy in patients allergic to penicillin

Cefuroxime (with or without additional metronidazole) was prescribed to 38%, 48% and 50% of patients with AT, PTA and PPA, respectively (Table 3). All remaining patients were given a macrolide, except one patient who was treated with clindamycin.

Adherence to antibiotic guidelines

The proportions of patients with AT, PTA, and PPA, who were prescribed antibiotics according to the guidelines, were 57%, 67%, and 65%, respectively (Table 2 and Table 3). The adherence rates were significantly lower in patients who were allergic to penicillin with AT (21%) and PTA (24%) than in non-allergic patients (AT 59% and PTA 68%) (both $p < 0.001$, Fisher's exact test).

Adherence rates for AT and PTA were high (81% and 82%, respectively) in the 2001-2005 period, but decreased significantly in the subsequent five-year period (to 34% and 47%, respectively) (both $p < 0.001$, Fisher's exact test). In the most recent period (2011-2014), adherence rates increased in patients with AT (55%) and PTA (65%) (both $p < 0.001$, Fisher's exact test). No significant differences in adherence rates for patients with PPA were found between time periods ($p = 0.58$ and $p = 1.00$, respectively).

Patient-related risk factors for adherence to antibiotic guidelines

Increasing age was significantly associated with non-adherence to guidelines in patients with AT ($p = 0.002$, Student's t-test) and PTA ($p < 0.001$) (Table 4).

In addition, male gender was significantly associated with non-adherence in patients with PTA ($p < 0.001$), and a similar trend was found in patients with AT ($p = 0.061$). Adjusted for gender, increasing age remained a significant risk factor for non-adherence in patients with AT ($p = 0.003$, logistic regression analysis) and PTA ($p < 0.001$). Similarly, male gender remained a significant risk factor for non-adherence in PTA patients when adjusting for age ($p = 0.004$). No significant risk factors were found in patients with PPA (gender: $p = 0.82$; age: $p = 0.08$).

Patients with AT and PTA who were treated in accordance with guidelines had significantly shorter duration of hospitalisation than patients treated non-adherently (Table 4, AT: $p = 0.039$ and PTA: $p < 0.001$, Student's t-test). Adjusted for age and gender, PTA patients who were treated with antibiotics according to

FIGURE 1



A CT scan of a 21-year-old male with peritonsillar abscess.

TABLE 3

Choice of antibiotic treatment in 88 patients with penicillin allergy admitted with pharyngeal infections in the 2001-2014 period. The values are n (%).

	Adherence	Non-adherence described reason	no described reason
<i>Acute tonsillitis (n = 34)</i>			
Cefuroxime:			
Cefuroxime + metronidazole			6
Macrolide ^a			13
Macrolide ^a + metronidazole			7
Cefuroxime + macrolide ^a			1
Subtotal	7 (21)	0	27 (79)
<i>Peritonsillar abscess (n = 50)</i>			
Tonsillectomy (n = 41):			
Cefuroxime	9		
Cefuroxime + metronidazole			11
Macrolide ^d			14
Macrolide ^d + metronidazole			6
Clindamycin			1
Incision & drainage (n = 9):			
Cefuroxime + metronidazole	3		1
Macrolide ^e			3
Macrolide ^e + metronidazole			2
Subtotal (n = 50)	12 (24)	0	38 (76)
<i>Parapharyngeal abscess (n = 4)</i>			
Cefuroxime + metronidazole	2		
Macrolide ^b + metronidazole			2
Subtotal	2 (50)	0	2 (50)
Total (N = 88)	21 (24)		67 (76)

a) Erythromycin (n = 10), clarithromycin (n = 1), roxithromycin (n = 1), azithromycin (n = 1); b) erythromycin (n = 5), clarithromycin (n = 2); c) clarithromycin (n = 1); d) erythromycin (n = 13), roxithromycin (n = 1); e) erythromycin (n = 4), clarithromycin (n = 1), roxithromycin (n = 1); f) clarithromycin (n = 2), roxithromycin (n = 1); g) Erythromycin (n = 2); h) Clarithromycin (n = 1), erythromycin (n = 1).

TABLE 4

Gender distribution, age and duration of hospitalisation in patients who were admitted with acute pharyngeal infections, stratified by antibiotic treatment according to guidelines (adherence versus non-adherence).

	Acute tonsillitis			Peritonsillar abscess			Parapharyngeal abscess		
	adherence	non-adherence	p-value	adherence	non-adherence	p-value	adherence	non-adherence	p-value
Male gender, %	43	49	0.06	51	59	< 0.001	65	61	0.82
Age, mean, yrs	26.7	29.9	0.002	23.6	29.6	< 0.001	45.3	37.3	0.08
Duration of admission, days	2.51	2.76	0.04	2.46	2.81	< 0.001	5.92	4.30	0.17

guidelines still had significantly shorter duration of hospitalisation ($p < 0.001$, logistic regression analysis), while no significant association was found in patients with AT ($p = 0.331$). No significant difference was found between adherence groups in patients with PPA (Table 4, $p = 0.17$, Student's t-test).

No significant associations between antibiotic adherence and infection markers (leukocyte count, neutrophil count, C-reactive protein) were found in patients with AT, PTA and PPA.

DISCUSSION

We found that 63% of patients with pharyngeal infections were prescribed antibiotics according to the local guidelines. The proportion of patients who were treated in agreement with the guidelines fluctuated significantly during the 14-year study period. However, the main reason for non-adherence throughout the period remained the same: metronidazole was prescribed to 878 (34.2%) patients, but only 117 patients (4.6%) should have been treated with metronidazole according to the guidelines. In addition, a significant proportion (53%) of penicillin-allergic patients were given macrolides instead of the recommended cefuroxime, which may be related to the fact that macrolides are recommended to penicillin-allergic patients with AT in general practice.

Disregarding the minority of patients with allergy to penicillin, broad-spectrum antibiotics were prescribed in only 69 (2.7%) cases. Hence, the lacking guideline adherence had limited impact on the selection of resistant bacteria, especially when the prescribed antibiotics are compared to recommendations from other researchers [11, 12]. In agreement with previous studies in other fields, we found that a significant proportion of doctors either disregarded or had no knowledge of the guidelines, but prescribed antibiotics as they believed was preferable [13-15]. There may be many (good) reasons for deviating from standard antibiotic regimens, but – going through the medical charts – we were able to find only four (0.4% of all the non-adherent prescriptions) cases with an explanation for the chosen, alternative treatment.

The excessive use of metronidazole in patients with severe AT and PTA is probably associated with the facts that the pathogens in these infections are unclarified and that some researchers recommend metronidazole for anaerobic coverage in the treatment of PTA [12, 16].

Revised antibiotic guidelines were introduced in October 2011 along with training in appropriate use of antibiotics for department clinicians. This increased focus on the guidelines is likely the reason for the observed subsequent increase in adherence. Studies suggest that interactive, small-group teaching and timely feedback are effective means in increasing adherence to (antibiotic) guidelines [3, 17, 18].

We found that increasing patient age (AT and PTA) and male gender (PTA) were independent risk factors for doctors' non-adherence to the guidelines. Interestingly, the mean duration of hospitalisation was lower in patients with AT and PTA, who were treated according to the guidelines than for patients who were treated with additional metronidazole or broad-spectrum antibiotics. This finding was highly significant for PTA patients, even after adjusting for age and gender. A potential explanation may be that these patients who were treated non-adherently to the conservative guidelines had more pronounced illness. However, no significant differences in infection markers (leukocyte count, neutrophils or C-reactive protein) were found between adherent and non-adherent patients in any of the three infection entities. With the caveat that other confounders may be present, our finding suggests that PTA (and possibly also AT) patients are better off when treated with penicillin G in monotherapy than when treated in combination with metronidazole. In a randomised, placebo-controlled trial, Wiksten et al. found that the addition of metronidazole to penicillin neither prevented nor enhanced recovery of PTA patients undergoing incision and drainage, but metronidazole was associated with significant side effects [19]. Similarly, Kieff et al found penicillin in monotherapy to be as effective as broad-spectrum antibiotics in PTA patients who were treated with incision and drainage [20]. To our knowledge, no other studies regarding the

effectiveness of different antibiotic regimens (exploring complications, duration and intensity of symptoms, the necessity for altered antibiotic treatment etc.) have been conducted in patients who were hospitalised with pharyngeal infections. Antibiotic recommendations based on bacterial findings in tonsillar surface swabs or pus aspirates from patients with these infections should be interpreted with great caution, as the majority of isolates may be insignificant bystanders. Hence, it is very likely that antibiotics covering all of the obtained bacteria are unnecessary. Studies on the significant pathogens in pharyngeal infections and preferable antibiotic regimens are warranted to reduce the antibiotic pressure (by reassuring clinicians that the pathogenic bacteria are covered) and for optimal patient recovery.

The present study has several limitations. We did not collect information regarding complications, adverse events or altered antibiotic regimens during hospitalisation. Therefore, our finding that penicillin alone was preferable to penicillin and metronidazole in PTA patients must be interpreted with caution. The number of patients treated non-adherently and without rational reasons for deviating from the guidelines may be overestimated, as some clinicians may not have described their reasons in the medical charts.

CONCLUSIONS

A significant (37%) proportion of patients with acute pharyngeal infections were treated non-adherently to antibiotic guidelines, mainly because of the addition of metronidazole to penicillin. Based on the literature on significant pharyngeal pathogens and our findings, the addition of metronidazole to penicillin seems inappropriate for treatment of patients with AT and PTA. We advocate continuous surveillance of antibiotic prescriptions on a departmental level to reduce unnecessary and inappropriate use.

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