Antibiotic therapy in non-gastrointestinal MALT lymphoma:
   a review of the literature

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Running title: Antibiotic therapy in non gastric MALT lymphoma

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Abstract:

While antibiotic therapy has been established as the standard of care in patients with gastric MALT lymphoma, much less is known about the value of antibiotic therapy in non-gastrointestinal (GI) MALT lymphomas.

A computerized (MEDLINE) accompanied by manual search to identify clinical reports on the topic of antibacterial therapy in patients with non-GI MALT lymphomas was performed.

The majority of data were available for MALT lymphoma of the ocular adnexa (OAML) including a total of 131 patients in 4 retrospective studies, three prospective series (including 81 patients) and one case report. Treatment was exclusively targeting Chlamyphila psittaci (CP), using doxycycline in all but two studies. The median follow-up for these studies was 25 months, and both CP-positive as well as patients tested negative responded. CR was achieved in 23 patients (18%), 36 (27%) had a PR, 55 (42%) had SD and 8 patients (6%) had progressive disease accounting for an ORR of 45%. In the largest study, a better response was suggested in CP-positive patients. By contrast, only scattered reports could be found for other non-GI localisations, allowing no conclusion about the benefit of antibiotic therapy and probably resulting in a publication bias towards positive cases.

Based on these results, antibiotic therapy using doxycycline appears to be a reasonable first line therapy for patients with MALT lymphoma of the ocular adnexa. Antibiotics, however, remain experimental for the time being in patients with other non-GI MALT lymphomas. Further preclinical studies as well as large scale therapeutic trials are warranted to define the role of antibiotic therapy in such patients.
Introduction:

Extranodal marginal zone B-cell lymphomas of the mucosa-associated lymphoid tissue (MALT lymphomas) represent about 8% of all B-cell lymphomas with a currently estimated world-wide prevalence of 2 / 100 000. While MALT lymphomas can develop in mucosal tissues throughout the entire body, gastric MALT lymphomas still constitute about 50% of new diagnoses. Further common sites include the ocular adnexa, salivary glands, and the lung but also rarer sites such as the skin, bladder, breast and highly “exotic” localisations like the dura mater, where the presence of acquired lymphoid tissue is difficult to explain [1,2].

Various contributing factors have been defined in terms of pathogenesis, including autoimmune diseases (e.g. Sjögren's syndrome and chronic autoimmune thyroiditis) particularly in women with lymphomas developing at extragastric sites [3], infections such as Hepatitis C virus in certain geographic areas [4,5], but most prominently bacterial infections exemplified by Helicobacter pylori (HP) in gastric MALT lymphoma. This close association has led to definition of antibiotic therapy as the standard approach to this cohort of patients. To the current knowledge, this antigenic-driven process involves the bacteria, but also auto-antigenic processing of B-cells within the gastric mucosa augmented by HP-specific T-cells featuring cross-reactivity with gastric auto-antigens resulting in the development of a specific monoclonal B-cell clone [6]. According to the literature, roughly 90% of gastric MALT lymphomas are associated with HP-infection, and HP-eradication has become the first line therapy in gastric MALT lymphoma including the rare cohort of HP-negative patients [7]. Several study groups in the last two decades have underlined the high efficacy of HP-eradication reporting long lasting complete remissions in up to 80% of patients without any need for more aggressive therapies in case of response to antibiotics [7-10].

While there is little doubt about the value of HP-eradication in gastric MALT lymphomas, a potential bacterial background in extragastric MALT lymphomas has been more difficult to establish. Conflicting data on the efficacy of HP-eradication in disseminated as well as localised extragastric MALT lymphomas have been published, mostly in the form of case reports and small
retrospective analyses. Apart from HP, Chlamydia (or more recently Chlamyphila) psittaci (CP) has been reported as a potential trigger for MALT lymphoma of the ocular adnexa (OAML) and a benefit of antibiotic treatment has been documented by Ferreri and coworkers [11]. In addition, Borrelia burgdorferi [12] as well as Campylobacter jejuni have been implicated in cutaneous MALT lymphoma and immunoproliferative intestinal diseases (IPSID) [13], a relatively rare variant of MALT lymphoma predominately found in the Middle East.

The objective of this article is therefore to summarize the currently published data on antibacterial treatment in non-gastrointestinal MALT lymphoma and to discuss the impact of these findings on the clinical management of such patients.
Methods:

A computerized search using MEDLINE was performed to identify available publications concerning antibiotic therapy in histologically verified non-gastrointestinal MALT lymphoma. Only articles with at least an English abstract were included, thus we cannot definitely exclude a minor bias due to non-provided / non-translated abstracts and published work with solely the abstract but not the full text online. Full-text publications were reviewed if written in English or German.

Articles concerning paediatric patients, e.g. under 18 years were not of interest for this review. No attempts to discover unpublished data were made. In addition to the computerized search in MEDLINE, a manual search in the reference sections of included papers was performed.

The following were the main points of interest for this review: detailed histological description of MALT lymphoma, number and basic characteristics (age, localisation and stage of disease) of reported patients; suspected pathogen as target for the antibiotic therapy; if assessed: serological / histological presence of pathogen and method of detection; line of therapy; route of administration, duration and dosage of antibiotic therapy; definition of response, overall response rate (ORR) and follow-up time. If available, we have also tried to extract the medical history of patients in terms of prior therapies.

Overall objective response was defined by the sum of complete (CR) plus partial remissions (PR) as reported by the authors. Furthermore, stable disease (SD), minimal response (MR) (less than 50% regression) and progressive disease (PD) were possible terms for outcome, but the further two were not included as remissions in our review. If the outcome was not classified within this ranking, we used the expression chosen by the author.
Results:

Ocular adnexal MALT lymphoma

Apart from Helicobacter pylori (HP), Chlamydia (or Chlamydophila) psittaci (CP) is the most intensively studied pathogen in MALT lymphoma, and has repeatedly been defined in MALT lymphoma of the ocular adnexa as a potential target for antibiotic therapy. In 2004 Ferreri and coworkers [11] were the first to report a possible association between CP and ocular adnexal MALT lymphoma and have consecutively contributed four further studies on CP eradication in such patients [14,17,18,21].

We could identify a total of nine studies [14-22] published between 2004 – 2012 on antibacterial therapy in patients with OAML including Korean, Italian, Hungarian, US-American, Chilean, Spanish, Swiss and Austrian study groups’ experiences, providing a more or less “global” overview. Taken together, a total of 131 patients were enrolled in these nine series, comprising four retrospective trials (number of patients = 58), one single case report, and three, (initially four) prospective trials including 81 patients. As the results from the 2005 Ferreri pilot project [21] are also part of the 2006 trial [18], these results were not considered separately in our further analysis.

The median follow-up time of these nine trials was 23 months (range; 1-62), and sufficient information about staging procedure and response criteria was available in all larger trials, though controversial findings with regards to the classification of bilateral orbital involvement were reported. Ferreri et al [17] rated bilateral disease in the ocular adnexa as stage IV, while Kim et al [16] considered the same extent of disease as stage I. Both authors yet refer to the Ann Arbor staging system. For the sake of this review, we have adopted the author's classification for further analysis.

For patients’ characteristics and details see Table 1. A median age of 55 years (range: 18-94) was reported in these trials (excluding the Ferreri et al 2012 trial data [14] where the median age of 60 years is given for all 47 patients registered, but not separately for the doxycycline-treated cohort),
and the stage at the beginning of antibacterial therapy was exclusively stage I in four studies, whereas the other studies have included various stages of OAML. One patient collective consisted only of disseminated stage IV patients, but these results were reported only in a brief letter to the editor [17].

CP status was determined in six out of nine studies [14-18,21] but remained unknown in two, resulting in “blind” antibiotic treatment in these latter series [19,20]. In addition, Chlamydia trachomatis was the present pathogen in the case report of Yeung et al [22]. Six of the study groups used touchdown enzyme time-release polymerase chain reaction (PCR) with the ability to detect CP DNA in either tumour tissues, peripheral blood monocytes or both [23], whereas the exact method of Chlamydia testing was not explained in the case report by Yeung et al [22]. In the most recent study, testing for CP was performed in lymphoma biopsies as well as blood and/or conjunctival swabs [14]. Out of the 116 patients tested within these studies, 66 (56%) showed a positive test result, while the others were rated negative for CP.

A single course of oral doxycycline at a dose of 100 mg given twice a day for three weeks was the most popular regimen and was used by most investigators [14,16-22]. By contrast, Kim and coworkers [16] added a second course after an interval of three weeks for patients with residual eye-related symptoms after the initial cycle. The activity of a six month oral application of 500 mg clarithromycin twice a day was assessed in an Italian pilot study [15], assuming potential additional direct anticancer effects of macrolide antibiotics through changes in apoptotic mechanisms of tumour cells. In addition, one patient received HP eradication as first line treatment for OAML.

As reported by the authors, a CR was achieved in 23 patients (18%) out of the collective of all 131 patients reported. Thirty-six (27%) had a PR, 5 (4%) were rated as MR or mild response, 55 (42%) as SD and 8 patients (6%) had progressive disease as assessed after finishing the respective treatment period. In summary, the numbers of CR and PR account for an ORR of 45%, excluding patients with a documented MR / mild improvement. However, one trial disclosed no response at all in 11 patients [19]. Response rates of different trials were comparable and in the range of 45%,
while the international phase II trial published in 2012 [14] had a notably better response at 65% in the treated collective.

Information on a potential influence of CP status on outcome is given in three trials, one reporting an equal response in both groups [16] while the two Ferreri et al trials found better results in CP positive patients (66% versus 50%, respectively 64% versus 38%, response rate) [14,18]. An association between Chlamydia eradication with response rate (86% in patients achieving clearance of CP versus 47%, p = 0.02) as well as with progression free survival at 5 years (68% versus 47%, p= 0.11) was documented in the most recent trial [14]. Regarding the single versus double course regimen used by Kim and coworkers [16], a trend towards better results in the double course regimen was stated.

In analogy to HP-eradication in gastric MALT lymphoma, trials with short follow-up might have underestimated the response to antibiotics, as Ferreri and coworkers [18] have emphasized the possibility of slow, respectively late responders showing best outcome after up to 36 months following therapy. By contrast, Grünberger et al [19] did not see any responses after a median observation time of nine months (range 7-14), and all patients underwent consecutive therapy with either chemotherapy or radiotherapy, which might have biased the findings against antibiotic therapy due to insufficient follow-up time.

Interesting results have been obtained with application of clarithromycin as used by Govi et al [15] who applied a six month regimen in patients with relapsed or refractory extranodal MALT lymphoma. This study was based on preclinical data proposing not only antibiotic but direct antineoplastic and immunmodulatory effects of macrolids as has been shown also in murine cancer models. Eleven patients with OAML and two further patients with either MALT lymphoma of the stomach and the breast, respectively, were included in the trial. However, an objective response was only achieved in patients with OAML. The overall response rate was 38%, respectively 45% in OAML and seems comparable to studies using doxycycline [16-18,21]. Remarkably, all patients included had been previously treated with doxycycline, but this had not resulted in lymphoma
regressions. Five patients had a history of chronic infection with CP or HP respectively which had been successfully eradicated 10 – 40 months before entering the study. Thus tumor regression due to elimination of bacteria may be ruled out and the authors suggest that the response achieved was based on the direct antitumoral activity of the drug and not by antimicrobial effects.

Five trials provide clear information about observed side effects and the toxicity of antibiotics was extremely low, as only a single case of grade II dizziness in a patient receiving doxycycline was reported and two cases with episodic grade I stomatitis and nausea in the clarithromycin trial [14-16,18,21].

In a retrospective analysis, Grünberger et al [24] have assessed the potential of HP-eradication to induce responses in patients with extragastric MALT lymphoma. Out of a total of 77 patients, 16 had undergone HP-eradication with metronidazole and clarithromycin as initial therapy for the lymphoma, including five patients with MALT lymphoma of the ocular adnexa. All patients were found to have evidence of HP-infection, but none of these patients responded to treatment and all required alternative therapy. Ferreri and coworkers [25] have assessed HP-status during staging in a group of 31 OAMZL patients. HP-positivity was documented in 10 patients (32%) and they were immediately treated with HP-eradication. None of the patients receiving HP-eradication responded with lymphoma regression to the eradication regimen, but three patients who had CP positive lymphomas received consecutive doxycycline which resulted in two CRs and one PR. This confirms again the non-activity of HP-eradication therapy in OAML patients and potential benefits of doxycycline irrespective of the persistence of HP infection.
“Other” non-gastrointestinal MALT lymphomas

While there is an accumulating body of data concerning antibiotic therapy of ocular adnexal MALT lymphomas, only scattered case reports of antibiotic therapy in other non-gastrointestinal localisations are available. Furthermore, no prospective controlled trials or larger studies have been published so far. Apart from a retrospective analysis performed at our institution [24] including 16 patients with extragastric MALT lymphomas (five ocular adnexal, six parotid, three pulmonary, one mammary and one colonic MALT lymphoma, respectively), an extensive search in MEDLINE resulted in a total of only 12 case reports. In the Austrian series, however, no responses were seen in these 16 patients who underwent HP-eradication for primary therapy of their lymphoma, and these patients are not further discussed.

The case reports detected in the literature have included MALT lymphomas localised in the skin, lung, parotid-, salivary- and thyroid glands, bladder and breast treated only with antibacterial therapy. For detailed information about the studies, patient’s characteristics (n=14) and therapeutic strategies see Table 2.

Cutaneous MALT lymphoma

Chronic infection with the gram-negative spirochet Borrelia (B.) burgdorferi is a known initiator of a characteristic cutaneous B-cell infiltration termed “pseudolymphoma” [26]. Due to a similar histological appearance, a potential role as a promotor for other B-cell lymphomas of the skin has been assumed [12]. In analogy with geographic incidence variations of CP positivity in OAMZL, endemic as well as nonendemic regions have been defined for this pathogen. Areas seen as endemic such as the Scottish Highlands or Austria have demonstrated up to 40% Borrelia infection in cutaneous marginal-zone lymphomas [12,27], while in a large Italian series by Ponzoni et al [28] no association was observed. In addition, a series of 60 cases of primary cutaneous marginalzone lymphoma collected in Germany, Asia and the United states found no evidence for Borrelia
infection [29]. Interestingly a French series (nonendemic region) found Borrelia DNA in 19% of 16 cases with primary cutaneous MALT lymphoma [30].

Antibiotic therapy for B. burgdorferi in cutaneous MALT lymphoma (also formerly related to as “skin-associated lymphoid tissue” (SALT) lymphoma) has been described in four case reports [31-34] comprising a total of five patients. Interestingly, in an additional case report amplified DNA of B. afzelii was found [35]. Three of these articles have been published in pathological journals and have thus concentrated on histopathological information rather than providing detailed clinical information. In addition, one article could only be obtained in abstract form. This paper was still included due to rarity of experiences and reports concerning antibacterial treatment of cutaneous MALT lymphoma [32]. In the four reports providing complete information [31,33-35], three patients were male and two were female, with patient's age being between 28 and 88 years. The detailed follow up time in months was given in four patients (see Table 2). Interestingly, one patient had a (histologically verified) history of lichen ruber planus [33] and in two other patients, erythematous papules and plaques had been present for more than a year [34]. In all patients, a detailed histological assessment of intralesional biopsies disclosed the presence of marginal zone B-cell lymphoma. An attempt to culture B. burgdorferi from affected skin was made in two studies, resulting in two positive results out of three patients; in the patient with a negative culture, a subsequent PCR for B. burgdorferi DNA was positive [33,34]. Serological testing for B. burgdorferi was performed using ELISA, though titres were only marginally elevated in two patients [34]. Extracutaneous manifestations were ruled out by regular staging procedures in all patients.

Treatment for B. burgdorferi or B. afzelii, as known for stage II or III Lyme disease was administered to all patients, i.e. i.v. application of two grams ceftriaxone daily for two or three weeks. This resulted in an initial PR in two patients, who were still improving at last follow-up and in another patient only residual infiltrations were seen in the final histological reassessment [31,33,35]. However, in the case reports of Küttting and coworkers [34], the standard ceftriaxone regimen did not result in regression of cutaneous MALT lymphoma and patients achieved CR only
after second line therapy with cefotaxime or third line therapy with intralesional interferon alpha-2a injections at a cumulative dosage of 64.5 million I.U. in a three week period. The sixth patient received antibiotic therapy stated as “specific antibiotic therapy for B. burgdorferi” in the abstract and was also rated as non-responding disease [32]. In the French series described above, one of the three detected Borrelia-associated cutaneous MALT lymphomas responded to antibiotic treatment, but no further clinical data on follow-up were available. [30]

In the context of antibiotic therapy in cutaneous MALT lymphoma, it has to be mentioned that a series published in 1991 has reported on 4 patients with cutaneous lymphomas given antibiotic therapy [36]. While one may speculate that these might indeed have been MALT-lymphomas, a definite diagnosis according to accepted pathohistological criteria can not be extracted from this paper.

Pulmonary MALT lymphoma.

As the lung is in almost continuous contact with the environment and potential pathogenic substances, one might assume that development of pulmonary lymphoma could be driven by bacterial or other infectious antigens. In a large analysis of 69 paraffin-embedded tissue blocks of primary pulmonary MALT lymphomas the frequency of Chlamydia infection (Cl. pneumoniae, Cl. trachomatis and Cl. psittaci) as well as the presence of Mycoplasma pneumoniae was assessed in pulmonary MALT lymphoma. However, the rate of Chlamydia-infection was judged to be below 20% and no evidence for mycoplasms was found, suggesting that these pathogens are rarely associated with pulmonary MALT lymphoma [37]. In contrast to this, another study assessed a total of five patients with pulmonary MALT lymphoma who all tested positive for CP, while no evidence for Cl. pneumoniae or trachomatis was detected [38]. Achromobacter xylosidans is another
potential candidate pathogen recently demonstrated in patients with pulmonary MALT lymphoma [39].

According to these data, the exact role of various pathogens in the lymphomagenesis of BALT lymphoma remains somewhat speculative and data on antibiotic therapy in patients with pulmonary MALT lymphoma are relatively scarce as no large consistent series have been published so far. Activity of antibiotic therapy has recently been reported by Ishimatsu and coworkers [40] who presented two cases of bronchus-associated lymphoid tissue lymphoma (BALT lymphoma). In one case, a 70 year old woman treated with combined chemotherapy followed by radiotherapy achieved only a small reduction of the tumor by these measures. In addition, consecutive long-term therapy with clarithromycin at a dose of 200 mg per day was given for co-existing chronic sinobronchial syndrome which - according to the authors - resulted in regression of the lymphoma. Another patient with Sjögren's syndrome and pulmonary MALT lymphoma showed regression immediately after HP-eradication therapy and improved to a CR while receiving long-term clarithromycin application at the same dosage.

According to our knowledge, these two patients are the only successful reports about antibiotics in pulmonary MALT lymphoma. While an effect of antibiotics on the lymphoma is indeed possible in the second patient, one has to be cautious in interpreting the results of the first patient who was been given antibiotics after combined chemo-radiotherapy. In fact, it has been shown that MALT lymphomas of the lung might show objective regression following therapy only after prolonged radiological follow-up, and this disease also might be prone to a spontaneous wax-and-wane phenomenon [41] making the interpretation of the authors difficult to verify.

Incidental diagnosis of pulmonary MALT lymphoma in a post-surgical histological specimen in a patient with Mycobacterium avium was published in 2004. In this patient, the lymphoma showed no evident recurrence after surgery though positive flow cytometry for bone marrow involvement and the authors have suggested this to be related to the long term antibiotic treatment for mycobacterial infection and that suppression of this chronic condition might have been crucial for the long-term
remission [42]. Again, this is difficult to verify, as surgery in limited stages of pulmonary MALT lymphoma has repeatedly been reported as effective therapy resulting in long-term remission by various authors, even in the absence of subsequent antibiotic therapy. In addition, no association between mycobacteria and MALT lymphoma has been reported to date, suggesting that the two conditions might in fact not have been related in this patient.

**MALT lymphoma of the thyroid gland and parotid gland**

MALT lymphomas both of the parotid as well as the thyroid gland often appear in a background of chronic autoimmune disease (e.g. Hashimoto's thyroiditis or Sjögren's syndrome), and the presence of an infectious trigger has therefore so far not been a common assumption. Thus, only three reports of single cases dealing with antibiotics in those lymphomas were available [43-45]. Two patients were female, one was male and the age ranged between 60 and 69 years. One patient had recurrent parotid MALT lymphoma presenting with stage I disease, another one MALT lymphoma involving both submandibular glands with additional lesions in the parotid, while the patient with thyroid MALT also had involvement of local lymph nodes, i.e. stage II. Concerning comorbidity, two patients had a known history of Sjögren's syndrome; one presented with Hashimoto's disease, hepatitis C virus infection and concomitant tubular adenocarcinoma of the stomach resulting in subtotal gastrectomy before therapy of MALT lymphoma. For staging, all patients underwent a gastroscopy to rule out gastric involvement, and histological assessment of gastric biopsies for HP was positive in all three cases. All three patients received HP eradication therapy resulting in complete remission of the lymphoma in all three cases. Combination of substances used were amoxicillin/clarithromycin plus a proton pump inhibitor (PPI) in two patients and doxycycline/metronidazole/bismuth plus PPI in another case (for exact dosing see Tab. 2). In view of the data published so far, one might potentially attribute the anti-lymphoma effect of the combinations including clarithromycin to direct antineoplastic rather than antibacterial effects. The
time to best response was six months in one patient with parotid MALT lymphoma and three weeks in the other, while no information was provided in the patient with salivary gland lymphoma. After a follow up time of 5, 22 and 48 months, none of the patients showed a relapse of the disease.

**MALT lymphoma of the bladder.**

Primary MALT lymphomas of the urinary bladder are exceedingly rare. Interestingly, we could still find three case reports on the topic of antibiotic therapy for primary management of MALT lymphoma of the bladder [46-48]. In one case report, only the abstract was in English while the original work was in Japanese [46]. The three patients reported in the literature were 59 - 78 years old, and the reported follow up time ranged between 19 and 36 months. Two patients presented with macrohaematuria, whereas the other one had a history of recurrent urinary tract infections with Escheria coli (E. coli) bacteria. In the two patients treated with HP-eradication therapy (exact dosing and substances not reported by the authors), HP was identified either by gastroscopy or serological assessment, and both patients subsequently developed a CR of their MALT lymphoma in the bladder. The third patient, who suffered from recurring E. coli infections received a combination of antibiotics for complicated urinary tract infections (trimethoprim, nitrofurantoin and cephradine for long-term treatment at a not specified dosage), and he also achieved a complete remission of the lymphoma.
MALT lymphoma of the breast.

In the prospective trial on oral clarithromycin as described earlier in this review, Govi et al [15] have not only included MALT lymphomas of the ocular adnexa (n=11), but also one patient each with gastric and one with mammary MALT lymphoma. The patient with MALT lymphoma of the breast was also treated with clarithromycin administered at a dose of 500 mg twice a day for six months. This patient had a long history of former therapies including combined chemotherapy according to the CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisolone) as first line, followed by radiotherapy twice, chlorambucil monotherapy and doxycycline (dosage unknown). In this patient, application of clarithromycin did not influence lymphoma growth, and the patient progressed during antibiotic therapy with the macrolide.
Discussion:

According to the data extracted from the literature, MALT lymphomas of various localisations have been treated with antibiotics, resulting in scattered case reports in most cases. The most solid data published exist for patients with ocular adnexal MALT lymphomas, where also preclinical data have been generated to support the use of antibiotics targeting CP as first line treatment.

Apart from the fact that CP has been demonstrated not only in lymphoma tissue, but has also been isolated from conjunctival swabs of such patients, the analogy between gastric MALT lymphoma / HP-infection and OAML / CP is also underscored by recent data on the immunoglobulin repertoire in OAML [49]. In this evaluation, it was shown that lymphoma cells express a distinct repertoire of immunoglobulins resembling auto-antibodies. In keeping with data from gastric MALT lymphoma associated with HP, the pathogens do not directly stimulate the malignant B-cells, but rather generate an inflammatory milieu which presents auto-antigens and thus drives expansion of malignant cells. In this environment, a preferential selection of IGHV genes, especially of the IGHV3 subgroup has been reported in this analysis. In HP-associated gastric MALT lymphoma, however, a “point of no return”, i.e. independence from the pathogens in lymphoma-growth and – maintenance has been shown, which is marked by t(11;18)(q21;q21) in the majority of cases. To the current knowledge, no such hallmark has been defined in OAML so far [7].

To date, a total of 131 patients have been published to have undergone antibiotic therapy consisting mostly of twice daily 100 mg doxycycline for 21 days. While the benefit from antibiotic therapy does not appear as pronounced as in gastric MALT lymphoma, these data clearly suggest a significant activity of antibiotics in OAML. According to the published results, activity was better in two of three studies in patients testing positive for CP, resulting in a response rate of 66% and 64% in the positive cohort, while it was 38% and 50%, respectively in the negative patients [14, 18]. These data nevertheless suggest that testing for CP might not be necessary in the clinical practice, as also patients with a negative CP-status might respond to therapy with doxycycline and
testing for CP has not been uniformly standardized so far. In addition, the side effects of this therapy were negligible, and doxycycline has been suggested as a reasonable first line therapy for patients with OAML [14]. Given the indolent natural course of the disease, this approach appears to be especially attractive as it might spare a significant cohort of patients the potential side effects of systemic therapy or radiation.

The efficacy of doxycycline, however, has been debated in the past, as various studies have not shown lymphoma regression in patients either given the tetracycline in an empiric way without prior testing for CP or also in a more controlled setting [19,20,22]. Various explanations for the discrepancy have been offered, including pronounced geographic variations in the incidence of CP infection [50]. While one might question the uncritical use of antibiotics targeting CP in areas with virtually absent infection-rate, in case of the study from our own institution, which did not find objective response to therapy in 11 patients with OAML [19], a note of caution has to be added, even though a recent series has found evidence for CP infection on 15% of OAML-samples [38]. One of the major caveats in interpreting these findings is the fact that the follow-up might simply have been too short for demonstration of remissions, as Ferreri and coworkers have repeatedly emphasized the potential for delayed response to therapy reflected by the median follows up of 37 months in the most recent series [14]. Based on the data presented so far, it appears reasonable to treat patients with OAML upfront with doxycycline if provided that patients are closely monitored in order to guarantee salvage therapy in case of non-response or progression. Whether doxycycline is indeed the antibiotic of choice nevertheless remains to be seen given recent data reported by Govi on the use of high-dose clarithromycin in MALT lymphoma [15]. Especially intriguing is the finding that also patient relapsing from or refractory to therapy with doxycycline have responded to clarithromycin, which appears to be highly concentrated in the conjunctival fluid of patients [15]. Whether this finding or an alternative, immunomodulatory property of the drugs is responsible for these results remains to be determined.
While the pioneering work of Ferreri and collaborators has firmly established OAML as potentially sensitive to antibiotic therapy, the data in other non-gastrointestinal MALT lymphomas are less clear. Recently, preclinical data have suggested that CP might also be of interest in other non-gastrointestinal MALT lymphomas. By using PCR amplification and direct sequencing in MALT lymphoma samples, Aigeslreiter et al [38] have detected evidence for CP-DNA in 5/5 lung samples (100%), 3/10 thyroid gland (30%), 2/15 salivary gland (15%), 2/13 OAML (15%) and 1/4 cutaneous (25%) MALT lymphomas. Especially the latter finding is intriguing, as the potential association between cutaneous MALT lymphoma and Borrelia-infection has not resulted in convincing clinical results. Though the numbers in some subgroups are small, these data warrant further assessment in order to form the rational basis for a potential clinical trials on anti-CP therapies in MALT lymphomas of these specific localisations. In addition, these results are in conflict with results published by Chanudet and co-workers [37], who have reported virtual absence of CP in patients with pulmonary MALT-lymphoma, and thus need further confirmation.

In addition, a recent large scale study by the IELSG has identified a high rate of infection with Achromobacter xylodosoxidans in pulmonary MALT lymphoma, but has only been published in abstract form so far [39]. A small pilot study applying broad-spectrum antibacterial PCR in samples from patients with hepatic MALT lymphoma has no identified evidence of bacterial infection [51]. To date, no prospective studies have been performed, and only small retrospective series or case reports applying different antibiotics have been published in various non-gastrointestinal MALT lymphomas, including lung, bladder, thyroid and salivary glands and breast. In view of this, one might suspect some publication bias, as negative results – especially if only single individuals or small number have been treated - are unlikely to have been reported. Furthermore the majority of patients received HP eradication including a macrolide antibiotic and one therefore might speculate that direct anti-neoplastic effects of clarithromycin might have played a profound role in the anti-lymphoma activity observed.
As a consequence, antibiotic therapy as front line therapy remains experimental for the time being with the exception of OAML (and of course gastric MALT lymphoma). In areas with a low rate of CP-infection, however, this approach might either be limited to asymptomatic patients in view of the indolent nature of MALT lymphoma or be based on CP-testing in patients with lymphoma threatening to impair the visual apparatus, if doxycycline is chosen. In addition, future studies with longer follow-up are necessary to establish the long-term activity of antibiotic treatment. As opposed to gastric MALT-lymphoma, where long term CRs, which may probably translate into cure of such patients have been firmly established, the data on antibiotics in non-gastric MALT lymphomas including OAML are not yet mature enough to draw definite long term conclusions. Studies on antibiotics are further hampered by the fact that potential infectious targets have yet to be identified in the large majority of localisations. To the current knowledge, only two pathogens, i.e. HP in gastric MALT lymphoma and CP in OAML have sufficiently been tested to allow a clear definition on the causative role of these two agents. Much weaker data exist for association between Borrelia and lymphomas, while other agents remain speculative at best for the time being. Prospective studies on the use of antibiotics based on preclinical findings are warranted in order to define a rational approach to the use of antibiotics in patients with MALT lymphomas of various localisations.

Authorship Contributions:

Both authors have designed and drafted the article and have performed search and review of the literature and have written and approved of the final paper.

Conflict of Interest Disclosure:

Both authors have no conflict of interest regarding the contents of the review to disclose.
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### Table 1. Therapy and outcome of antibiotic therapy targeting CP in ocular adnexal MALT lymphoma.

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<th>First author</th>
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<th>No. of patients</th>
<th>Median age</th>
<th>Stage</th>
<th>CP pos</th>
<th>Previous therapies</th>
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<td>NA</td>
<td>I</td>
<td>29 (94%)</td>
<td>none</td>
<td>doxycycline 100 mg BID x 21d</td>
<td>22 (65%)</td>
<td>66% / 50%</td>
<td>CR 6 (18%), PR 16 (47%), SD 11 (32%), PD 1 (3%)</td>
<td>37 (15-62)</td>
</tr>
<tr>
<td>Govi [15]</td>
<td>prospective</td>
<td>11</td>
<td>57 (36-80)</td>
<td>IV</td>
<td>4 (36%)</td>
<td>yes</td>
<td>clarithromycin 500 mg BID x 6m</td>
<td>5 (45%)</td>
<td>NA</td>
<td>CR 2 (18%), PR 3 (27%), SD 3 (27%), PD 3 (27%)</td>
<td>25 (12-35)</td>
</tr>
<tr>
<td>Kim [16]</td>
<td>retrospective</td>
<td>38</td>
<td>47</td>
<td>I</td>
<td>15 (39%)</td>
<td>none</td>
<td>doxycycline 100 mg BID x 21d (n=12/38) alone or same followed by a second course after 21d off (n=26)</td>
<td>18 (47%)</td>
<td>60% / 60%</td>
<td>CR 7 (18%), PR 11 (29%), SD 20 (53%) (5 patients progressed consecutively)</td>
<td>26 (6-44)</td>
</tr>
<tr>
<td>Ferreri [17]</td>
<td>retrospective</td>
<td>6</td>
<td>70 (49-87)</td>
<td>IV</td>
<td>6 (100%)</td>
<td>yes**</td>
<td>doxycycline 100 mg BID x 21d</td>
<td>2 (33%)</td>
<td>NA</td>
<td>CR 0 (0%), PR 2 (33%), MR 1 (11%), SD 1 (11%), PD 2 (33%)</td>
<td>31 (7-56)</td>
</tr>
<tr>
<td>Ferreri [18]</td>
<td>prospective</td>
<td>27</td>
<td>56 (29-87)</td>
<td>I-IV</td>
<td>11 (41%)</td>
<td>ND</td>
<td>doxycycline 100 mg BID x 21d</td>
<td>13 (48%)</td>
<td>64% / 38%</td>
<td>CR 6 (22%), PR 7 (26%), MR 3 (11%), SD 9 (33%), PD 2 (7%)</td>
<td>14 (3-45)</td>
</tr>
<tr>
<td>Grünberger [19]</td>
<td>retrospective</td>
<td>11</td>
<td>63 (40-94)</td>
<td>I-IV</td>
<td>ND</td>
<td>none</td>
<td>doxycycline 100 mg BID x 21d</td>
<td>0 (0%)</td>
<td>NA</td>
<td>SD 11 (100%)</td>
<td>9 (7-14)</td>
</tr>
<tr>
<td>Abramson [20]</td>
<td>retrospective</td>
<td>3</td>
<td>70 (58-79)</td>
<td>ND</td>
<td>ND</td>
<td>none</td>
<td>doxycycline (n=2): 100 mg BID x 28d, 500 mg clarithromycin and 500 mg amoxicillin BID x 14d (n=1)</td>
<td>3 (100%)</td>
<td>NA</td>
<td>CR 2 (66%), PR 1 (33%)</td>
<td>34 (18-42)</td>
</tr>
<tr>
<td>Ferreri [21]†</td>
<td>prospective</td>
<td>9</td>
<td>72 (52-87)</td>
<td>I-IV</td>
<td>9 (100%)</td>
<td>yes††</td>
<td>doxycycline 100 mg BID x 21d</td>
<td>4 (44%)</td>
<td>NA</td>
<td>CR 2 (22%), PR 2 (22%), SD 1 (11%), MR 3 (33%), PD 1 (11%)</td>
<td>12 (1-31)</td>
</tr>
<tr>
<td>Yeung [22]</td>
<td>case report</td>
<td>1</td>
<td>18</td>
<td>ND</td>
<td>C.t.° pos</td>
<td>none</td>
<td>doxycycline 100 mg BID x 21d</td>
<td>mild improvement</td>
<td>NA</td>
<td>mild improvement 1 (100%)</td>
<td>6</td>
</tr>
</tbody>
</table>

**former therapies of patients included: surgery (n=1); CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) (n=1, stage IV), chlorambucil followed by COP (cyclophosphamide, vincristine and prednisone) and radiotherapy (n=1, stage IV), topical antibiotic (n=2), doxycycline (n=11)**

**doxycycline for first line (n=2), second line (n=2), third line (n=2); previous therapies not closer described by the author**

†† patients of this study were also part of the 2006 Ferreri et al trial [18]

° patient tested positive for Chlamydia trachomatis

†† former therapies of patients included: CEP (cyclophosphamide, epidoxorubicin, vincristine, prednisone) (n=1), radiotherapy (n=4), corticosteroids (n=1), topic interferon (n=1), interferon alpha-2b (n=1), chlorambucil (n=1), rituximab (n=1), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) (n=1)

CP = Chlamydophila psittaci, C.t. = Chlamydia trachomatis, ND = no data, BID = twice a day, d = day, m = month, pos = positive, neg = negative, NA = not applicable, ORR = overall response rate, CR = complete remission, PR = partial remission, SD = stable disease, PD = progressive disease
Table 2. Antibiotic therapy in other non-gastrointestinal MALT lymphomas: study and patient characteristics.

<table>
<thead>
<tr>
<th>First author</th>
<th>No. of patients</th>
<th>Localisation</th>
<th>Stage</th>
<th>Pathogen</th>
<th>Previous therapies</th>
<th>Therapy</th>
<th>Detailed outcome</th>
<th>FUP (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fühler [31]</td>
<td>1 (F/80)</td>
<td>skin</td>
<td>I</td>
<td>B. burgdorferi</td>
<td>none</td>
<td>ceftriaxone i.v. 2 g a day x 14d</td>
<td>minimal residuals</td>
<td>ND</td>
</tr>
<tr>
<td>Monari [32]</td>
<td>1 (ND)</td>
<td>skin</td>
<td>ND</td>
<td>B. burgdorferi</td>
<td>none</td>
<td>“specific antibiotic therapy for B. burgdorferi”</td>
<td>no response</td>
<td>ND</td>
</tr>
<tr>
<td>Roggero [33]</td>
<td>1 (M/72)</td>
<td>skin</td>
<td>I</td>
<td>B. burgdorferi</td>
<td>none</td>
<td>ceftriaxone i.v. 2 g a day x 14d</td>
<td>PR</td>
<td>22</td>
</tr>
</tbody>
</table>
| Küttting [34]| 2 (M/28, M/38)  | skin         | I     | B. burgdorferi | none              | 1<sup>st</sup> line: ceftriaxone i.v. 2 g a day x 14d, doxycycline 200 g a day x 21d  
2<sup>nd</sup> line: cefotaxime pulse therapy (i.v. 4 g TID x 2d, every 8 days, x 8 cycles) | PR               | 14/7         |
| Aberer [35]  | 1 (F/88)        | skin         | I     | B. afzelii    | none              | ceftriaxone i.v. 2 g a day x 21d                                         | PR               | 25           |
| Ishimatsu [40]| 2 (F/70, F/57) | lung         | ND    | ND / HP pos   | yes / none        | clarithromycin 200 mg a day as long-term treatment (in one patient only after HP-eradication therapy) | CR 1, PR 1       | ND           |
| Iwai [43]    | 1 (F/60)        | parotid gland | I     | HP pos        | none              | omeprazole, amoxicilline and clarithromycin x 7d                         | CR               | 48           |
| Arima [44]   | 1 (M/69)        | thyroid gland | II    | HP pos        | none              | amoxicillin 1500 mg a day, clarithromycin 400 mg and lansoprazole 60 mg; daily x 14d | CR               | 5            |
| Alkan [45]   | 1 (F/62)        | salivary gland | II    | HP pos        | none              | doxycycline 100 mg, metronidazole 500 mg, omeprazole 20 mg and bismuth 100 mg; all TID x 14d | CR               | 22           |
| Fujimura [46]| 1 (F/69)        | bladder       | ND    | HP pos        | none              | antibiotic treatment for urinary tract infection, HP-eradication         | CR               | 25           |
| Van den Bosch [47]| 1 (M/59) | bladder       | I     | HP pos        | none              | HP-eradication                                                          | CR               | 36           |
| Oscier [48]  | 1 (F/78)        | bladder       | ND    | Escheria coli | none              | trimetoprim, nitrofurantoin and cephradine (long-term)                   | CR               | 19           |
| Govi [15]    | 1               | breast        | IV    | ND            | 5<sup>th</sup> / 6<sup>th</sup> line** | 5<sup>th</sup> line: doxycycline,  
6<sup>th</sup> line: clarithromycin 500 mg BID x 6m | PD               | ND           |

* former therapies of first patient included: CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), radiotherapy

** former therapies of patient included: CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), twice radiotherapy, chlorambucil, doxycycline, and clarithromycin

ND = no data, B. = Borrelia, HP = Helicobacter pylori, i.v. = intravenously, d = day, TID = three times daily, BID = twice daily, CR = complete remission, PR = partial remission, PD = progressive disease, FUP = follow-up
Antibiotic therapy in non-gastrointestinal MALT lymphoma: a review of the literature

Barbara Kiesewetter and Markus Raderer