

# A Retrospective Study: Acne Vulgaris with Oral Antibiotic Treatment at Dermatovenereology Outpatient Clinic Dr. Soetomo General Hospital Surabaya

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**Keywords:** Acne Vulgaris, Doxycycline, Oral Antibiotic, Lehmann, Plewig and Kligman

**Abstract:** Introduction: Acne vulgaris (AV) is a common skin disease, affecting more than 85% of adolescents and often continuing into adulthood. The pathogenesis of acne involves 4 main processes: follicular hyperproliferation, excess sebum production, inflammation, and proliferation of *Propionibacterium acnes*. Although acne vulgaris is not an infection, the normal resident, *Propionibacterium acnes*, is the stimulus for inflammation in acne vulgaris, and a reduction in *P. acnes* populations is usually accompanied by clinical improvement. **Objective:** The aim of this study is to evaluate the use of oral antibiotic treatment in patients with acne vulgaris at dermatovenereology outpatient clinic dr. Soetomo general hospital. **Methods:** This is a retrospective study which analyze the data from medical records. **Result:** Among 475 patients, 63,37% has been diagnosed AV moderate or AV Papulopustular grade 3-4. Doxycycline is the first choice oral antibiotic used to treat Acne Vulgaris, used in 98,53% cases, with the duration between 4-8 weeks in 54,36% cases. There are good improvement, shown as decline severity index in diagnosis (before oral antibiotic treatment is AV moderate at 65,37% and after treatment is AV mild at 68,90%), after the patients get the treatment. **Conclusion:** Doxycycline is effective as first line oral antibiotic to treat moderate and severe acne vulgaris in Dr. Soetomo general hospital.

## 1 INTRODUCTION

Acne vulgaris is a chronic inflammatory dermatosis notable for open or closed comedones (blackheads and whiteheads) and inflammatory lesions, including papules, pustules, or nodules (also known as cysts) (Collier, *et al.*, 2007). AV is a multifactorial inflammatory disease affecting the pilosebaceous follicles of the skin. The current understanding of AV pathogenesis is continuously evolving. Key pathogenic factors that play an important role in the development of AV are follicular hyperkeratinization, microbial colonization with *Propionibacterium acnes*, sebum production, and complex inflammatory mechanisms involving both innate and acquired immunity. In addition, studies have suggested that neuroendocrine regulatory mechanisms, diet, and genetic and nongenetic factors all may contribute to the multifactorial process of AV pathogenesis (Zaenglein, *et al.*, 2016).

AV is a common skin disease, especially in adolescents and young adults. AV affects approximately 85% of teenagers, but can occur in most age groups and can persist into adulthood. There is no mortality associated with AV, but there is often significant physical and psychological morbidity, such as permanent scarring, poor self-image, depression, and anxiety (Lehman, *et al.*, 2002). Antibiotic therapy is a time-honored practice in AV treatment. Although AV is not an infection, the normal resident, *Propionibacterium acnes*, is the stimulus for inflammation in acne, and a reduction in *P. acnes* populations is usually accompanied by clinical improvement. Many AV patients is effectively treated with the use of long-term antibiotic regimens, and the practice is generally considered to be safe and effective (Webster and Graber, 2008). The aim of this study is to evaluate the use of oral antibiotic treatment in patients with AV at dermatovenereology outpatient clinic dr. Soetomo general hospital.

## 2 METHODS

This study is a retrospective study that analyze the data of AV that we get based on medical record during January 2013 until December 2015. We only analyze the new patients who got oral antibiotic as one of the treatment choice in dermato-venereology outpatient clinic.

## 3 RESULTS

There were 2.525 new patients who diagnosed with AV and got treatment from Dermato-venereology outpatient clinic in Dr. Soetomo General Hospital, Surabaya from 2013 until 2015. There were 475 patients (18,81%) given oral antibiotic. Table 1 shown the distribution of the diagnose and therapy. Of 475 patients, 301 patients (63,37%) has been diagnosed AV moderate or AV Papulopustular grade 3-4. Doxycycline is the most frequent oral antibiotic used to treat AV in Dr. Soetomo General Hospital.

From 475 patients with oral antibiotic treatment, only 283 patients (59,75%) control to dermato-venereology outpatient clinic. Of 283 patients, 195 patients show a good improvement during the second visit (data not shown). The duration of the

treatment depends on the amount of visitation recorded. Most of them, 54,36%, have the treatment between 4-8 weeks. The detail is shown in Table 2.

Figure 1 shows the comparison diagnose before and after oral antibiotic treatment. AV moderate was the most diagnose made before the treatment (185 among 283 patients, 65,37%) while after the treatment most patients was diagnosed as AV mild (195 among 283 patients, 68,90%).

## 4 DISSCUSSION

AV is a multifactorial, pleomorphic skin disease of the pilosebaceous follicles characterized by a variety of noninflamed (open and closed comedones) and inflamed (macules, papules, pustules and nodules) lesions. Microcomedones (earliest subclinical lesions) are thought to be the precursor lesions that can then develop into non-inflamed and / or inflamed lesions. Although a common disease, the etiology of acne is not yet fully elucidated and is thought to be a multifactorial process. Androgens, excessive sebum production, hyper-proliferation and abnormal differentiation of the follicular infundibulum, changes in the microbial flora, as well as inflammation and immunological

Table 1: Diagnose and Therapy of Acne Vulgaris.

Information	Amount	Percentage (%)
<b>Diagnose / AV Severity</b>		
AVMild*/ Komedonal-Papulopustular grade 1-2**	68	14,31
AV Moderate*/Papulopustular grade 3-4**	301	63,37
AV Severe*	53	11,16
AV Konglobata**	53	11,16
Total	475	100
<b>Therapy</b>		
Doxycycline	468	98,53
Erythromycin	4	0,84
Clindamycin	2	0,42
Cefixime	1	0,21
Total	475	100

\*) Lehmann Criteria \*\*) Plewig and Kligman Criteria

Table 2: Durations of Treatment.

Duration of treatment	Amount	Percentage (%)
<4 weeks	87	30,74
4-8 weeks	140	49,48
9-12 weeks	6	2,12
13-18 weeks	6	2,12
>18 weeks	7	2,47
Without data	37	13,07
Total	283	100

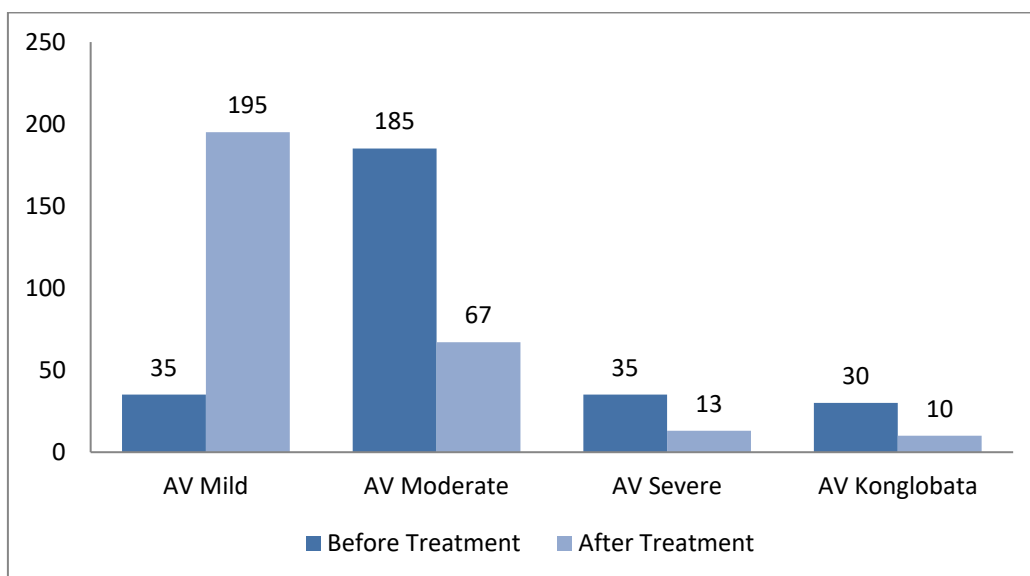


Figure 1. Distribution of AV diagnose before and after treatment.

host reactions are considered the major contributors to acne pathogenesis (Shaheen and Gonzales, 2012).

Plewig and Kligman divide AV into three categories, (1) comedonal acne, (2) papulopustular acne, and (3) acne conglobata. Comedonal acne mean that the lesions are dominantly open and closed comedones. Some inflammatory lesions may be, and frequently are present, but there are never more than five on one side of the face. The severity of comedonal acne is measured as grade I: less than 10 comedones on one side, grade II : 10-25 comedones on one side, grade III: 25-50 comedones on one side, grade IV: above 50 on one side. Papulopustular acne is by far the commonest type in mid adolescence. Actually, it is a mixture of comedones and inflammatory lesions which are either pustules or papules. Assignment to this category is based solely on the prevalence of inflammatory lesions, regardless of the number of comedones. Grade I: less than 10 on one side, grade II: 10-20 on one side, grade III: 20-30 on one side, grade IV: more than 30 on one side. By definition, acne conglobate is never mild. The disease is usually appeared with nodul and cystic form with severe inflammation.<sup>6</sup> Lehmann also divides AV into three categories, (1) mild, (2) moderate, and (3) severe. Mild acne character is <20 comedones, or <15 inflammatory lesions, or total lesion count <30. Moderate acne is 20-100 comedones, or 15-50 inflammatory lesions, or cyst < 5, or total lesion count 30-125. Severe acne >5 cysts, or total comedones count >100, or total inflammatory count >50, or total lesion count > 25. Inflammatory lesion in Lehmann categories is papul

and pustul (Lehmann, *et al.*, 2002)

From Table 1, we can see that most of the patients is diagnosed with AV moderate in Lehmann categories, equivalent with papulopustular grade 3-4 in Plewig and Kligman categories. Before 2015, Plewig and Kligman criteria was used to diagnose acne vulgaris in Dr. Soetomo general hospital. After Kelompok Studi Dermatologi Kosmetik Indonesia (KSDKI) set Lehmann criteria as standard criteria to diagnose acne vulgaris, we used Lehmann criteria at Dr. Soetomo general hospital. This is the reason there were some differentiations in acne vulgaris diagnose at dermato-venereology outpatient's medical records during 2013-2015.

Without treatment, acne is generally expected to spontaneously regress during the late teenaged or early adulthood years. However, a significant number of patients experience persistent acne or develop new-onset adult acne after adolescence (Collier, *et al.*, 2007). Systemic antibiotics have been a mainstay of acne treatment for years. They are indicated for use in moderate to severe inflammatory acne and should be used in combination with a topical retinoid and Benzoyl Peroxide. Evidence supports the efficacy of tetracycline, doxycycline, minocycline, erythromycin, and azithromycin to treat AV (Zaenglein, *et al.*, 2016).

The tetracycline class of antibiotics, including doxycycline and minocycline as second generation of tetracycline, should be considered first-line therapy in moderate to severe acne, except when contraindicated because of other circumstances (ie,

pregnancy, below 8 years of age, or allergy). The antibiotics of the tetracycline class work by inhibiting protein synthesis by binding the 30S subunit of the bacterial ribosome. This class also has notable anti-inflammatory effects, including inhibiting chemotaxis and metalloproteinase activity (Zaenglein, *et al.*, 2016). Tetracycline, often dosed at 500 mg twice daily for acne, must be taken on an empty stomach (1 hour before eating or 2 hours after eating). Ingestion with food and especially dairy products can block the absorption of tetracycline in the gut. Tetracycline can frequently cause gastrointestinal upset and may very rarely cause esophagitis and pancreatitis (Webster and Graber, 2008). Doxycycline, a second-generation member of the tetracycline family, is often dosed at 100 mg twice daily to give optimal antibacterial effects. Unlike tetracycline, doxycycline may be taken with food. However, doxycycline has more potential to induce a phototoxic reaction than tetracycline and extreme care should be used when prescribing doxycycline in the summer months (Webster and Graber, 2008). According to Kelompok Studi Dermatologi Kosmetik Indonesia (KSDKI) and Panduan Praktik Klinis Perhimpunan Dokter Spesialis Kulit dan Kelamin Indonesia (PERDOSKI), doxycycline is a first line oral antibiotic to treat AV moderate with the dose 50-100 mg, 1-2 times daily (Wasitaatmaja, *et al.*, 2016; Anon, 2017). In Dr. Soetomo dermatovenereology outpatient clinic, doxycycline was used as oral antibiotic treatment in 98,53% AV patients.

Another second-generation tetracycline, minocycline, is also commonly dosed at 100 mg twice daily for acne, although 1 mg/kg has been shown to be an effective dosage for the average acne patient and one with fewer side effects. Like doxycycline, minocycline can be taken with food. Unlike the other tetracyclines, the minocycline chemical structure has a large side chain that increases its side effect profile. Because of the high lipophilicity of minocycline, it can cross the blood-brain barrier and may induce vestibular disturbances, such as dizziness, vertigo, and ataxia. A blue-gray discoloration of the skin may be seen with long-term minocycline use. Rarely, minocycline may induce a serum sickness-like reaction characterized by arthralgias, urticaria, fever, and lymphadenopathy. When this occurs, it typically starts just days to weeks after beginning minocycline. Other less common side effects of minocycline include drug induced lupus-like disease, vasculitis and hepatic failure (Webster and Graber, 2008). Erythromycin and azithromycin have also been used in the

treatment of acne. The mechanism of action for the macrolide class of antibiotics is to bind the 50S subunit of the bacterial ribosome. Again, there are some anti-inflammatory properties for these medications, but the mechanisms are not well understood. Azithromycin has been primarily studied in the treatment of acne in open label studies with different pulse dosing regimens ranging from 3 times a week to 4 days a month, with azithromycin being an effective treatment in the time span evaluated usually 2 to 3 months. A recent randomized controlled trial comparing 3 days per month of azithromycin to daily doxycycline did show superiority of doxycycline (Zaenglein, *et al.*, 2016). Beside the high use of doxycycline in dermatovenereology outpatient clinic, there were 7 patients (1,47%) using other classes of oral antibiotics, such as erythromycin, clindamycin, and cefixime. The consideration of using different class of oral antibiotic usually depends on the history of doxycycline allergy, pregnancy and lactation. Unfortunately, there were not enough documentation in these 7 patient's medical record.

The intensity of doxycycline penetration is excellent in the pilosebaceous unit, and it takes 6-7 days to reach the pilosebaceous gland. Doxycycline works long-term with a half-life of 18-22 hours. Therefore, the duration of oral antibiotic therapy for AV cases is a minimum of 6-8 weeks, a maximum of 12-18 weeks. The expected clinical effects take 4-8 weeks. If an individual does not respond to antibiotics or stops responding, there is no evidence that increasing the frequency or dose is helpful. Such strategies increase selective pressure without increasing efficacy. Antibiotics should be stopped if no further improvement is evident. Antibiotics should not be routinely used for maintenance. Global Alliance to Improve Outcomes in acne (2003) recommends that if antibiotics must be used for longer than 2 months, benzoyl peroxide should be used for a minimum of 5-7 days between antibiotic courses to reduce resistant organisms from the skin (Williams, *et al.*, 2012). The use of doxycycline in AV management at Dr. Soetomo general hospital is already appropriate with the guideline. The dose and duration is correct to treat AV moderate or worse. From Figure 1, it is concluded that using doxycycline is giving a good result in AV patient because there are a significant decrease in AV severity (before treatment: AV moderate 65,37% and after treatment AV moderate: 23,68%, AV mild: 68,90%).

The choice of antibiotic should therefore be based on the patient's preference, the side-effect

profile, and cost. Clinicians also should pay attention to pharmacokinetic factors that influence the absorption and tissue distribution for individual antibiotic agents to better inform on rational dosing considerations of oral antibiotics for the treatment of acne vulgaris (Leyden and Rosso, 2011). A general problem with the tetracycline derivative is the potential for photosensitivity. Doxycycline was believed to impair the effectiveness of many types of hormonal contraception due to CYP450 induction. Recent research has shown no significant loss of effectiveness in oral contraceptives while using most tetracycline antibiotics (including doxycycline), although many physicians still recommend the use of barrier contraception for people taking the drug to prevent unwanted pregnancy. Doxycycline is categorized by the FDA as a class D drug in pregnancy. As with all tetracycline antibiotics, it is contraindicated in pregnancy through infancy and childhood below eight years of age, due to the potential for disrupting bone and tooth development. Doxycycline crosses into breast milk. Although the dose an infant would receive through breastfeeding would likely be minimal, it is better to not give doxycycline to breastfeeding mothers (Zaenglein, *et al.*, 2016). Although the tetracycline can function in many ways to be beneficial, the physician should be well versed in the potential side effects of these drugs. This detail side effect, interaction, and pregnancy and lactation status were not well recorded in dermato-venereology outpatients clinic so that we could not evaluate any further to this condition.

## 5 CONCLUSIONS

The used of doxycycline as first line oral antibiotic at dermato-venereology outpatient clinic, Dr. Soetomo general hospital is already appropriate the guideline and effective to treat acne vulgaris. The suitable dose and duration also play an important role of the successful treatment. We recommend to continue using doxycycline as the first line oral antibiotic treatment for acne vulgaris.

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