



# Therapeutic Options

## FOCUS ON ACNE

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Acne vulgaris, often referred to as acne, is one of the most common skin disorders and one of the most burdensome across the globe.<sup>1,2,3</sup> It is a chronic, inflammatory, dermatologic condition that can affect patients both physically and psychologically.<sup>2,4,5,6,7</sup> Physically, acne lesions may result in disfigurement and permanent scarring; emotionally, acne can cause depression, anxiety and low self-image.<sup>1,2,3,4,5,8</sup> Therapeutic goals of acne treatment focus on promptly and effectively clearing and preventing lesions and reducing scarring and dyspigmentation, and to reduce the impact on quality of life.<sup>2,3,9,10</sup> The following will review current recommendations for acne therapy, as well as tips for helping patients manage this condition.

### ETIOLOGY & PATHOPHYSIOLOGY

Acne may occur at any age, although it usually begins in adolescence.<sup>2,4</sup> In patients between 12 to 24 years of age, prevalence is estimated to be approximately 85%. Acne has a variable age of resolution, and despite treatment may persist into adulthood.<sup>3,4,9</sup> The negative effect of acne on mental health can greatly affect a patient's quality of life, with increases in prevalence of mood disorders, suicidality, psychiatric hospitalizations, school absenteeism and unemployment.<sup>9</sup>

Although our understanding of the pathologic mechanisms and treatment options for acne continue to evolve, it is clearly multifactorial.<sup>2,4,6,7</sup> Four key elements are thought to contribute to acne pathogenesis: abnormal follicular

hyperkeratinization, excess sebum production, *Cutibacterium acnes* (previously *Propionibacterium acnes*) proliferation, and multiple immune inflammatory mechanisms.<sup>2,4,5,8</sup>

Acne may be the result of several endocrine disorders such as polycystic ovarian syndrome, androgen secreting tumours, Cushing's syndrome due to prolonged corticosteroid use, or excess hormones (androgens, insulin, glucocorticoids, growth hormone). Drugs that may induce acne include glucocorticoids, testosterone, phenytoin, phenobarbital, lithium and isoniazid.

Other factors to consider for the cause of acne include topicals (oily cosmetics), diet (sugar, dairy), environmental factors (heat, humidity, sunlight, hairstyle, clothing) and stress.<sup>17,18,19</sup>

There are six phylotypes of *C. acnes*, a normal element of the skin microbiome. However, in acne pathogenesis this population seems to shift, with some of these phylotypes stimulating more inflammatory cytokines than others. *C. acnes* can activate an innate immune response in the skin, stimulate sebaceous glands, and influence keratinocyte differentiation. Some of the phylotypes form biofilms which may be less susceptible to antibiotic treatment. Normalizing the phylotype ratio while maintaining the skin's microbiome may be a potential treatment goal in the future.<sup>8</sup>

### SIGNS & SYMPTOMS

Acne presentation varies in type, severity and distribution of lesions.<sup>2</sup> Type of lesions

include open or closed comedones (blackheads or whiteheads, respectively) and inflammatory lesions, which may include pustules (large collections of neutrophils), papules, cysts (keratin-filled dilated structures), or nodules (palpable, red, tender lesions).<sup>3,4,5</sup>

Currently there is no universal grading system for acne severity.<sup>11</sup> However, in general, mild or **comedonal acne** presents as small, white or grey-white papules (closed and open comedones, respectively) and pustules, which are usually scattered with limited skin involvement and lack of nodules or scarring.<sup>2,3,11</sup> **Mild to moderate papulopustular acne** will exhibit several papules, pustules, and some nodules (primarily superficial lesions). **Severe inflammatory acne** may present with multiple papules, pustules, numerous nodules, cysts, and scarring; these deeper pustules or nodules may be painful and cover larger areas.<sup>2,3</sup> Similar conditions include rosacea, periorificial dermatitis, milia, sebaceous hyperplasia, folliculitis, and drug reactions and must be excluded.<sup>2</sup>

### PHARMACOTHERAPY

Clinical practice guidelines in Canada recommend acne therapy based on acne severity.<sup>3</sup> Acne lesion types, severity, complications (such as scarring, post-inflammatory hyperpigmentation, psychological distress) and contributing factors (such as skin care products, acne-inducing medications, etc.) must all be considered when selecting therapy.<sup>11</sup> Treating acne with a combination of medications will help target the various aspects of acne pathogenesis.<sup>6</sup> Options for topical therapy include benzoyl

peroxide (BPO), retinoids, antibiotics, salicylic acid, glycolic acid, azelaic acid, and dapsone. If there is an inadequate response after 2-3 months of topical therapy or if acne lesions become more apparent and inflammatory, or if acne is moderate to severe, a systemic agent may be required.<sup>2,5</sup> Oral acne therapy options include antibiotics, isotretinoin, and hormonal therapy (combined oral contraceptives [COCs], spironolactone).

On June 15, 2023, Health Canada authorised Winlevi (clascoterone) for the topical treatment of acne vulgaris in patients aged >12 years.<sup>20,21</sup> Winlevi is the first and only topical Androgen Receptor Inhibitor to target the hormonal component of acne. Winlevi should be reserved for patients in whom initial topical therapies fail; for moderate to severe acne, it may be used as part of an appropriate combination regimen.

With either topical or systemic acne therapies, it may take 4-8 weeks or longer to see any improvement. Evaluation of therapy efficacy should take this into account.<sup>1,2,3</sup>

Therapeutic options are discussed below based on acne severity. For a general treatment algorithm, see Figure 1. For details on specific medications, see Table 1 and Table 2.

#### **Comedonal (Mild) Acne**

First-line therapy for comedonal acne is either a topical retinoid or BPO. Alternatively, a combination of topical medications such as fixed-dose adapalene/BPO or clindamycin/BPO may be chosen as initial therapy.<sup>3,6</sup>

If there is an inadequate response after 2-3 months of use, a topical retinoid may be added if not yet part of therapy, or alternate therapies such as a clindamycin/tretinoin topical combination, a combined oral contraceptive (COC) in women, an alternate topical retinoid, or topical dapsone may be considered.<sup>3,6</sup>

#### **Mild to Moderate Papulopustular Acne (Localized)**

The degree of inflammation and distribution of lesions may vary in this population. All three of the above options (topical retinoids, BPO, and fixed-dose topical combinations) are strongly recommended. First-line recommendations include BPO or a topical retinoid as monotherapy. Topical fixed-dose combination treatment of clindamycin/BPO or adapalene/BPO may also be used initially, as generally these combinations are superior to their individual components. An alternative combination of topical clindamycin/tretinoin may also be tried. If acne is covering an extensive or hard-to-reach area (e.g., the back), a systemic medication may be added to topical treatment.<sup>3</sup>

#### **Moderate Papulopustular Acne (Extensive)**

In addition to the topical medications as described above for papulopustular acne, an oral antibiotic may be added for extensive lesions. Tetracycline or doxycycline are the preferred options, as minocycline is associated with an increased risk of serious side effects (such as drug-induced lupus and hepatitis). Antibiotics for acne therapy should not be used alone due to the development

of bacterial resistance.<sup>3</sup> If appropriate, in women a COC may also be added to the topical medications noted above.<sup>3,6</sup>

#### **Severe Acne**

In cases of severe acne, oral isotretinoin is strongly recommended. Prescribers should be trained and experienced in its use, due to the risks of teratogenicity and adverse events. In patients unable to use oral isotretinoin, an oral antibiotic combined with BPO (with or without a topical retinoid) may be an option. COCs may also be considered for eligible women.<sup>3</sup> Oral tetracycline with topical adapalene has been found to be equally as effective as oral isotretinoin for deep inflammatory lesions (e.g., nodular or conglobate acne), but not for non-inflammatory or superficial inflammatory lesions.<sup>3,12</sup> In one study, the combination of oral doxycycline and topical adapalene/BPO was comparable to oral isotretinoin for severe nodular acne, although it was unlikely to induce acne remission and demonstrated a decreased effect in reducing baseline lesion count compared to oral isotretinoin.<sup>3,13</sup> Alternative options for severe acne include switching the oral antibiotic or adding spironolactone in eligible females.<sup>6</sup>

#### **SPECIFIC PATIENT POPULATIONS**

Acne in **children** under seven years of age may be an indication of hyperandrogenism and should be investigated.<sup>11</sup> Preadolescent children may be treated with topical adapalene, tretinoin, tazarotene or BPO; however, avoid tetracyclines in patients under 8 years of age.<sup>1,4,6</sup> During pregnancy, topical BPO, topical clindamycin or

**Figure 1. Management of acne<sup>4</sup>**

Acne Severity	First-line Choices	Second-line Choices
<b>Mild</b>	<b>One of the following:</b> BPO Topical retinoid Topical combination therapy*	<b>One of the following:</b> Add BPO or topical retinoid (if not already using) Alternate retinoid Topical dapsone Winlevi (clascoterone)
<b>Moderate</b>	<b>One of the following:</b> Topical combination therapy* BPO + topical retinoid + oral antibiotic BPO + topical retinoid + topical antibiotic + oral antibiotic	<b>One of the following:</b> Alternate combination therapy Alternate oral antibiotic Add COC or oral spironolactone (female) Oral isotretinoin Winlevi (clascoterone)
<b>Severe</b>	<b>One of the following:</b> Oral antibiotic + topical combination therapy* Oral isotretinoin	<b>One of the following:</b> Alternate oral antibiotic Add COC or oral spironolactone (female) Oral isotretinoin Winlevi (clascoterone)

BPO=benzoyl peroxide; COC=combined oral contraceptive.  
\* Topical combination therapy is either: BPO + antibiotic, BPO + retinoid, or BPO + antibiotic + retinoid.

**Table 1. Topical medications for the treatment of acne vulgaris**<sup>1,2,3,4,5,6,9,11,14,20,21</sup>

Topical Options	Place in Acne Therapy	Action and Onset	Key points	Counseling tips
<b>Benzoyl peroxide (BPO)</b>	<ul style="list-style-type: none"> <li>Mild: monotherapy</li> <li>Mild, moderate, severe: combination therapy with topical retinoid +/- topical antibiotic</li> </ul>	<ul style="list-style-type: none"> <li>Bactericidal activity by oxidizing bacterial proteins</li> <li>Eliminates and prevents <i>C. acnes</i> on skin and in sebaceous follicles</li> <li>Mild comedolytic</li> <li>Mild anti-inflammatory</li> <li>Fast onset: results in as few as 5 days</li> </ul>	<ul style="list-style-type: none"> <li>Using BPO with antibiotics improves efficacy</li> <li>Available OTC</li> <li>Inexpensive</li> <li>Higher doses may not be more effective but may increase irritation</li> <li>No resistance reported</li> </ul>	<ul style="list-style-type: none"> <li>Mild irritant (dryness, redness, peeling): best to start with 2.5% or 5% strength; can also suggest non-comedogenic moisturizer</li> <li>Can test small patch of skin for sensitivity before using on larger area</li> <li>Try every other day if irritation, then increase to daily</li> <li>Can bleach hair/clothing; patients should be aware so precautions can be taken</li> </ul>
<b>Retinoids</b> (Tretinoin, adapalene, tazarotene, trifarotene; combination products with other ingredients)	<ul style="list-style-type: none"> <li>Preferred treatment and maintenance for all forms of acne</li> <li>Comedonal (mild): monotherapy for initial treatment; adapalene or tazarotene superior to tretinoin</li> <li>Mild-moderate papulopustular: tazarotene equivalent or superior to adapalene</li> <li>Mixed/inflammatory: use with topical/oral antibiotic</li> <li>Moderate/severe inflammatory: add oral antibiotic</li> </ul>	<ul style="list-style-type: none"> <li>Vitamin A derivatives</li> <li>Most powerful comedolytics</li> <li>Regulate proliferation/differentiation of keratinocytes, normalize skin shedding, anti-inflammatory</li> <li>Onset: may take months to see effect</li> </ul>	<ul style="list-style-type: none"> <li>Decreases long-term risk of pigmentation issues and collagen damage that may lead to scarring</li> <li>Minor differences in efficacy between retinoids; strength/vehicle more important factors</li> <li>If inadequate response to one retinoid, change in strength, formulation, or type may help</li> <li>Tretinoin most photosensitizing, but most cost-effective</li> <li>Adapalene least irritating, more effective and better tolerated than tretinoin</li> <li>Tazarotene most potent; more effective than tretinoin but more irritating and costly</li> <li>Trifarotene limited evidence compared to other retinoids; expensive</li> <li>Micronized gel tretinoin formulation (<i>Retin-A Micro</i><sup>®</sup>) may be better tolerated</li> </ul>	<ul style="list-style-type: none"> <li>Apply at different time of day from BPO unless in a combination product (to avoid decrease in retinoid stability)</li> <li>Can cause dryness, burning, peeling, erythema, stinging, scaling, irritation; start with low strength and/or apply less frequently e.g. 3x weekly and build up to nightly basis</li> <li>Advise use of noncomedogenic moisturizer</li> <li>Apply at night and use daily sunscreen (photosensitizing)</li> <li>Can be helpful to continue topical retinoid (for maintenance) after stopping oral therapy</li> <li>Not recommended in pregnancy</li> </ul>
<b>Antibiotics</b> (Clindamycin, erythromycin)	<ul style="list-style-type: none"> <li>Can use first-line but not as monotherapy</li> <li>Papulopustular acne</li> <li>Mild-severe: combination therapy with BPO +/- topical retinoid</li> </ul>	<ul style="list-style-type: none"> <li>Decreases <i>C. acnes</i> by accumulating in follicle and exerting anti-inflammatory mechanisms</li> </ul>	<ul style="list-style-type: none"> <li>Combine with BPO to reduce risk of antibiotic resistance and increase efficacy</li> <li>Clindamycin most common, preferred over erythromycin due to better efficacy</li> <li>Fixed-dose combination with BPO may increase compliance</li> </ul>	<ul style="list-style-type: none"> <li>Consider therapy washout after 3 months to limit resistance</li> </ul>
<b>Glycolic acid</b>	<ul style="list-style-type: none"> <li>Can use when retinoids not tolerated</li> </ul>	<ul style="list-style-type: none"> <li>Alpha-hydroxy acid</li> <li>Mild comedolytic</li> <li>Keratolytic</li> </ul>	<ul style="list-style-type: none"> <li>Available OTC</li> </ul>	
<b>Azelaic acid</b>	<ul style="list-style-type: none"> <li>Mild-moderate acne</li> <li>Can use to reduce post-inflammatory dyspigmentation as it lightens skin</li> </ul>	<ul style="list-style-type: none"> <li>Mild comedolytic</li> <li>Antibacterial</li> <li>Anti-inflammatory</li> <li>Inhibits tyrosinase to improve post-inflammatory hyperpigmentation</li> </ul>	<ul style="list-style-type: none"> <li>When used as monotherapy, similar effect as adapalene or BPO</li> <li>Similar tolerability as adapalene, better tolerated than BPO</li> <li>Useful adjunct for post-inflammatory pigmentation</li> </ul>	<ul style="list-style-type: none"> <li>Mildly irritating</li> </ul>
<b>Salicylic acid</b>	<ul style="list-style-type: none"> <li>Mild acne, particularly in patients with sensitive skin</li> </ul>	<ul style="list-style-type: none"> <li>Comedolytic</li> <li>Keratolytic, opens comedones</li> </ul>	<ul style="list-style-type: none"> <li>Higher than 2% usually irritating</li> <li>Better tolerated than BPO or tretinoin, less effective</li> <li>Available OTC (0.5%-2% strengths)</li> </ul>	
<b>Dapsone</b>	<ul style="list-style-type: none"> <li>Mild: monotherapy, or instead of topical antibiotic in combination regimen</li> <li>Moderate-severe: instead of topical antibiotic in combination regimen</li> <li>Inflammatory acne, particularly in adult women</li> </ul>	<ul style="list-style-type: none"> <li>Synthetic sulfone, acts on inflammatory cascade that results in nodules, cysts and erythema</li> </ul>	<ul style="list-style-type: none"> <li>More beneficial in women than men/adolescents</li> </ul>	<ul style="list-style-type: none"> <li>Mildly irritating</li> <li>Using in combination with BPO causes orange discoloration (secondary to oxidation) of skin; can be washed or brushed off</li> </ul>
<b>Clascoterone (Winlevi)</b>	<ul style="list-style-type: none"> <li>Use if initial topical therapies fail; for moderate to severe acne, it may be used as part of an appropriate combination regimen.</li> </ul>	<ul style="list-style-type: none"> <li>Inhibits effects of androgen receptors in cells of the sebaceous glands to reduce sebum production and inflammatory cytokines</li> </ul>	<ul style="list-style-type: none"> <li>Winlevi is rapidly metabolized in the skin, limiting systemic absorption, thus suitable for males</li> <li>Pediatric: Children may absorb proportionally larger amounts and more prone to systemic effects, use limited to &gt;12 years</li> </ul>	<ul style="list-style-type: none"> <li>Local adverse effects: erythema, redness, pruritus, dryness, scaling</li> </ul>

BPO=benzoyl peroxide; OTC=over-the-counter

**Table 2. Oral medications for the treatment of acne vulgaris.**<sup>1,2,4,5,6,7,8,9,15,16</sup>

Oral options	Place in Acne Therapy	Action and Onset	Key points	Counselling tips
<b>Antibiotics</b> (Tetracyclines: doxycycline, minocycline, tetracycline; macrolides, SMX/TMP, trimethoprim, amoxicillin, cephalixin)	<ul style="list-style-type: none"> <li>Mild inflammatory: in combination with topical products, particularly for hard-to-reach areas</li> <li>Moderate-severe, inflammatory: when topical products ineffective; can use in addition to BPO or topical retinoid</li> </ul>	<ul style="list-style-type: none"> <li>Inhibit bacterial growth through various mechanisms</li> <li>Onset: may take 1-2 months to see improvement, 3-4 months for maximum effect</li> </ul>	<ul style="list-style-type: none"> <li>Not used as monotherapy</li> <li>Tetracyclines first-line for moderate to severe acne</li> <li>Doxycycline and minocycline more effective than tetracycline; typically doxycycline is recommended</li> <li>Minocycline has been associated with increased risk of hepatitis, drug-induced lupus, DRESS, hypersensitivity reactions; tinnitus, dizziness; more serious AEs compared to other tetracyclines</li> <li>Due to resistance concerns, macrolides or SMP/TMX only used if tetracyclines not effective, contraindicated or not tolerated</li> <li>Limit to 3 months if possible (briefest time frame) and continue topical product</li> <li>Stop once appearance of new inflammatory lesions is reduced but continue with topical product(s)</li> <li>If no apparent improvement after 12 weeks, seek alternate therapy</li> </ul>	<ul style="list-style-type: none"> <li>May need to trial for at least 6 weeks to see effect</li> <li>Use with BPO to reduce risk of bacterial resistance, and use BPO or retinoid for maintenance when antibiotic no longer required</li> <li>Can take doxycycline with food if GI upset occurs</li> <li>Severe AEs from oral antibiotics for acne are uncommon</li> <li>Avoid tetracyclines in pregnancy and in patients under 8 years of age</li> <li>Tetracyclines can cause photosensitivity; use of sunscreen is recommended</li> </ul>
<b>Isotretinoin</b>	<ul style="list-style-type: none"> <li>Severe nodular, cystic, or inflammatory acne</li> <li>Moderate acne when other therapies fail</li> <li>Acne resulting in scarring/causing distress</li> </ul>	<ul style="list-style-type: none"> <li>Decreases sebum and scarring</li> <li>Comedolytic, anti-inflammatory</li> <li>Only therapy that can potentially cure acne</li> </ul>	<ul style="list-style-type: none"> <li>Isomer of retinoic acid</li> <li>Most powerful anti-acne therapy</li> <li>Can clear acne and produce sustained remission even in severe cases</li> <li>Low doses may also be effective and are associated with fewer AEs</li> <li>Weight-based dosing; often a lower dose is used for first month, then increased afterwards as tolerated</li> <li>Treatment duration is often around 20 weeks</li> <li>Measure LFTs, serum cholesterol and triglycerides at baseline, repeat until responding to treatment</li> </ul>	<ul style="list-style-type: none"> <li>Potent teratogen; baseline and monthly pregnancy tests need to be done for women of child-bearing age, must use contraception (2 methods) until 1 month post-treatment</li> <li>Best absorbed with food</li> <li>AEs include dry skin, lips, eyes, nosebleeds, myalgias and usually stop when medication discontinued</li> <li>Can suggest moisturizers, lip balms etc. to aid with dryness</li> </ul>
<b>COCs</b> (estrogen and progestin)	<ul style="list-style-type: none"> <li>For mild acne with topical failure, moderate acne, or as an adjunct in severe acne (in teen girls and women)</li> <li>Inflammatory acne in eligible females</li> <li>Alone or in combination with other acne therapy</li> </ul>	<ul style="list-style-type: none"> <li>Antiandrogenic effects (net effect of all COCs; however, cyproterone acetate or drospirenone are specifically antiandrogens)</li> <li>Decrease function and size of sebaceous glands</li> <li>Reduce counts of inflammatory and comedonal lesions</li> <li>Onset slow, improvement by end of cycle 3</li> </ul>	<ul style="list-style-type: none"> <li>In some females, acne may flare with menstrual cycle</li> <li>COCs indicated for acne treatment include ethinyl estradiol/norgestimate, ethinyl estradiol/drospirenone</li> <li>Preferred COC options are those with progestin with less androgenic activity, or those with a higher estrogen dose</li> <li>Cyproterone acetate/ethinyl estradiol may help women with severe acne unresponsive to other therapy</li> </ul>	<ul style="list-style-type: none"> <li>COCs can be associated with VTEs (risk may be higher with anti-androgens), CV risk, increased risk of breast cancer or cervical cancer; important to ask about smoking, family history, thromboembolism history</li> </ul>
<b>Spirolactone</b>	<ul style="list-style-type: none"> <li>Used primarily in women with cyclic acne or androgenization</li> </ul>	<ul style="list-style-type: none"> <li>Antiandrogenic; aldosterone receptor antagonist that decreases testosterone production</li> </ul>	<ul style="list-style-type: none"> <li>Quality evidence lacking; prescribed off-label for acne treatment</li> <li>Dose range 25mg - 200mg daily</li> <li>Caution using with drospirenone-containing oral contraceptives due to an overlap of similar activity</li> <li>Check DHEAS and free testosterone at baseline then every 3 months</li> </ul>	<ul style="list-style-type: none"> <li>May need to monitor blood pressure</li> <li>Side effects are dose related (menstrual irregularity, breast tenderness/enlargement, fatigue, diuresis)</li> <li>Generally well tolerated at low doses</li> </ul>

AEs=adverse events; BPO=benzoyl peroxide; COC=combined oral contraceptive; DHEAS=dehydroepiandrosterone sulfate; DRESS=drug reaction with eosinophilia and systemic symptoms; GI=gastrointestinal; LFTs=liver function tests; SMP/TMX=sulfamethoxazole and trimethoprim

topical erythromycin are considered safe. Azelaic acid and glycolic acid both have low systemic absorption and are not likely to be a risk to fetal growth.<sup>2</sup> If an oral antibiotic is required, erythromycin (not the estolate salt) is considered safe; tetracyclines should be avoided.<sup>1,2</sup> Oral isotretinoin and topical tazarotene are contraindicated; other topical retinoids are not recommended during pregnancy.<sup>11</sup> Topical antibiotics, BPO, topical retinoids, azelaic acid, and glycolic acid are compatible with breastfeeding.<sup>2</sup>

## THERAPEUTIC TIPS

- Often a combination of acne medications (whether topical or oral) may be required for optimal acne management.

- Topical medications should be applied across the affected area of skin, rather than just the lesions, in order to prevent new lesion development.<sup>2</sup>
- Minimize topical irritation of products by starting with less frequent application, lower strengths and shorter contact time, then slowly increase as tolerated.<sup>2</sup>
- A cream or lotion may be preferred for patients with dry or sensitive skin, whereas oilier skin may prefer a gel.<sup>1,3</sup>
- Topical fixed-dose combination products and once daily applications may improve patient adherence.<sup>3</sup>
- Antibiotics (topical or oral) should not be used as monotherapy due to the risk of developing antibiotic resistance.<sup>6</sup>

Strategies to decrease the risk of bacterial resistance include limiting duration of treatment and combining with topical treatments (like BPO).<sup>1,3</sup>

- Once acne is controlled with combination topical and systemic therapy, systemic therapy may be discontinued and topical therapy continued for maintenance.<sup>2</sup>
- Isotretinoin may induce prolonged remission.<sup>2</sup>
- Acne therapy is often prematurely discontinued due to early improvement, appearance of worsening acne, or side effects;<sup>9</sup> these are important counselling points to help patients understand the importance of adhering to a specific regimen for therapeutic success.

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