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Class Update: Tetracyclines

Date of Review: March 2017 **Date of Last Review:** May 2015

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
Current Oregon Health Plan (OHP) fee-for-service (FFS) drug policy for tetracyclines limit the use of these antibiotics to one 14-day supply every 6 months to prevent use for non-funded conditions like acne or rosacea. However, this drug policy may cause unnecessary delay therapy in patients with skin and soft tissue infections (e.g., MRSA infections), osteomyelitis, or other conditions like chronic suppression for non-removable infected prostheses or other foreign body. A class update will be performed with the purpose of identifying if there is a need to change the current drug policy.

Research Questions:
1. Is there evidence to support extended therapy of tetracyclines beyond 14 days? For which clinical indications does the evidence support extended use?
2. Are there any safety concerns when using extended therapy of tetracyclines for chronic suppression or other indications?
3. Is there any new evidence for differences in efficacy or effectiveness or safety between the tetracycline agents?

Conclusions:
- There is no new comparative evidence for differences in efficacy/effectiveness or safety between tetracycline antibiotic formulations.
- There is insufficient evidence to support extended use of tetracycline antibiotics beyond 14 days outside of acne and rosacea. However, some exceptions may include bacillary angiomatosis, glanders, and bone and joint infections (e.g., osteomyelitis) for those not candidates for surgical intervention.
- There is insufficient evidence to support differences in safety or efficacy of Doryx® (doxycycline hyclate delayed-release tablets) and other oral delayed-release doxycycline formulations.
- There is insufficient evidence to address the safety of extended therapy with tetracycline antibiotics. Tetracyclines should generally be avoided in pregnant women or children under the age of 8 years.
- Doxycycline is the most commonly used tetracycline and is recommended as first- or second-line options for multiple indications or as part of combination therapy based on low quality evidence.
- From 7/1/2016 to 9/30/2016, there were 45 denied claims that did not result in a PA request and treatment was not received. Of the 27 denied claims for preferred products, 44% (n=12) of claims were associated with an unfunded condition (acne, rosacea, Hidradenitis suppurativa) and were prescribed for more than 14 days. The remaining claims were associated with funded conditions, including skin and soft tissue infections and upper respiratory tract infections.

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Recommendations:

- Evaluate comparative costs in executive session.
- Change quantity limit to allow two 14 day supplies in a 3 month timeframe.

Previous Conclusions:

- Doxycycline is the most commonly recommended tetracycline and is recommended for multiple indications as first line, second line, or as part of combination therapy based on limited, low quality evidence.
- Tetracycline is recommended for select indications based on expert opinion and low quality evidence.
- Minocycline is a potential agent for methicillin-susceptible *S. aureus* (MSSA) and MRSA in non-pregnant adults and children over 7 years based on limited, low quality evidence.
- The majority of members (69.2%) received a single prescription with an average of a 13-day supply. A minority of members (17.8%) received more than two tetracycline prescriptions.
- Most tetracycline claims were for short-term therapy (57%), followed by medium-term duration (28%) and long-term duration (15%).
- Members with claims data indicating treatment of tetracyclines for only unfunded conditions comprised 27.9% of the total study population and represented 43.3% of the total prescription drug expenditures ($28,439).
- When a funded condition for a tetracycline was identified, 86% of members received only short-term treatment.

Previous Recommendations:

- Restrict use of all (preferred and non-preferred) tetracycline antibiotics to a 14-day supply every 6 months.
- Make tetracycline antibiotic therapy exceeding 14 days every 6 months subject to prior authorization to verify the presence of an OHP funded condition.

Background:

Tetracycline antibiotics work by entering the bacterial cell wall, binding reversibly to the 30s ribosomal subunit to inhibit protein synthesis.[1] They are indicated for a variety of infections caused by many aerobic gram-positive and gram-negative bacteria, including sexually transmitted diseases, respiratory tract infections, urinary tract infections (UTI), skin and soft tissue infections (SSTI), acne vulgaris, rosacea, as well as a variety of less common infections (e.g., anthrax). For most indications, duration of treatment does not exceed 14 days. Extended therapy is indicated most commonly for acne and rosacea.[2] Rosacea and most mild forms of acne fall below the current Oregon Health Plan (OHP) funded line on the Prioritized List of Health Services.[3] The only funded form of acne is acne conglobata in the presence of recurrent abscesses or communicating sinuses. [3] In the tetracycline class, doxycycline is one of the most active agents and used most often clinically. Doxycycline can be administered twice daily, has both intravenous and oral formulations, can be given with food, and is less likely to cause photosensitivity. However, the spectrum of activity is similar between the agents in the class. Tetracyclines should generally be avoided in pregnant women or children under the age of 8 years.[1] Recent changes in generic manufacturing of tetracyclines has resulted in significant price increases for both oral tetracycline and oral doxcycline products.[4]

Demeclocycline is a tetracycline that antagonizes the actions of vasopressin at the collecting duct in the nephron, producing diuresis by inhibiting ADH-induced water reabsorption in the distal portion of the convoluted tubules.[5] The use of demeclocycline is limited to treatment of Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

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In 2015, a drug use evaluation of OHP FFS patients showed that the majority of members (69.2%) received a single prescription per year with an average 13-day supply dispensed.[6] Approximately 28% of prescriptions were associated with unfunded diagnoses and a small number (15%) of members received chronic therapy. As a result of this, a policy was implemented to restrict use of all tetracyclines to a 14-day supply every 6 months to limit extended therapy for unfunded conditions. Claims that exceed this limit require prior authorization to confirm treatment for an OHP-funded condition. [6]

Tetracyclines are one of the few classes with oral agents available to cover community-acquired methicillin resistant *staphylococcus aureus* (MRSA).[7] Current Infectious Disease Society of America (IDSA) guidelines recommend doxycycline as a preferred empiric treatment option for purulent moderate skin and soft tissue infections (SSTI) when MRSA is suspected or confirmed.[8] Other oral options include clindamycin and sulfamethoxazole-trimethoprim. However, resistance rates are higher for clindamycin than the other agents. Treatment duration of tetracyclines for common conditions is usually 5-10 days. According to the guidelines, a duration of longer than 14 days is only recommended for the treatment of bacillary angiomatosis and glanders, in which treatment can extend up to 6 months. For recurrent skin abscesses, an additional 5- to 10-day course of an active antibiotic is recommended. Additionally, due to the excellent bioavailability of doxycycline, IDSA guidelines recommend it as an oral treatment option for vertebral osteomyelitis.[9] Duration of therapy for osteomyelitis can extend to 3 months. For those with osteomyelitis not suitable for surgery, long-term suppressive therapy may be used after initial parenteral therapy. For bone and joint infections caused by *staphylococcus aureus* in patients who not candidates for surgical intervention, up to 6-12 weeks of combination therapy with doxycycline can be considered.[7,10] Uncomplicated cystitis or pyelonephritis due to MRSA is uncommon and extended therapy of tetracyclines is not routinely recommended for the treatment of complicated or uncomplicated urinary tract infections.[11]

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

A systematic review from the Cochrane Collaboration was completed in 2015 to assess the efficacy and safety of treatments for rosacea.[12] Overall, oral tetracycline and low dose doxycycline (40 mg) were associated with improvements in populopustular rosacea compared with placebo and isotretinoin was associated with improvement compared to doxycycline. There is high quality evidence from 2 studies that oral doxycycline (40 mg) compared to placebo was associated with 2 grades of improvement among 90 of 269 participants (33% vs. 21%; RR 1.63; 95% CI 1.22-2.18) over 16 weeks. [12] There was no statistically significant difference in effectiveness between 100 mg and 40 mg doxycycline, but there were fewer adverse effects with the lower dose (RR 0.25; 95% CI 0.11 to 0.54) Evidence only supports doxyxcline for papulopustular rosacea (subtype 2). [12] Currently rosacea falls below the funding line on the Oregon Health Plan's prioritized list.

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Guidelines:
None identified.

New Safety Alerts:
None identified.

New Formulations or Indications:
In May, 2016 the FDA approved Doryx® MPC (doxycycline hyclate) delayed-release (DR) tablets for the treatment of rickettsial infections, sexually transmitted infections, respiratory tract infections, other bacterial infections, ophthalmic infections, anthrax, severe acne and prophylaxis of malaria.[13] It is available as 60 mg and 120 mg DR tablets. This new formulation was approved around the same time doxycycline hyclate DR tablets became available as a generic tablet. Doryx® MPC incorporates a modified polymer coat designed to further delay the release of doxycycline. Doryx® MPC 120 mg is equivalent to doxycycline DR 100 mg and 60 mg MPC is equivalent to 50 mg due to a reduced bioavailability. There is no evidence of clinical superiority of Doryx MPC compared to doxycycline delayed release. Approval was based on pharmacokinetic data from phase 1 clinical trials.[14]

Randomized Controlled Trials:
A total of 30 citations were manually reviewed from the literature search. After manual review, 30 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical).

Drug Use Evaluation:

Methods:
FFS paid and denied claims were evaluated from 7/1/2016 and 9/30/2016 to determine the disposition of the PA and potential effects from the quantity limit (Table 1). Categories are mutually exclusive but members requesting different medications during the reporting period may be counted on more than one row. Claims that resulted in no drugs within the class paid for within 90 days of the index event (first request) were further evaluated for a follow up PA or reason for no paid claim (Table 2). Members with Medicare plans were excluded. Patient profiles for denied claims with no PA requested were further reviewed for diagnosis and duration.

Results:
Table 1 includes data on requests for tetracycline antibiotics including paid claims or paid claims for an alternative in the class. The majority of claims were for doxycycline, a preferred product. Approximately 60% of claims resulted in paid drug claim for the requested product or an alternative in the class within 90 days. However, the other 40% (n=260) resulted in no paid claim within 90 days after the index event, with a little over half of those from non-preferred agents (doxycycline tablet and minocycline). Of those claims that did not result in drug treatment, 75% of those can be explained by another source of payment (Table 2). A PA was never requested after a total of 45 claims (17%), which could be a result of the quantity limit in place. Only 8 of the PA requests were denied.

For preferred products only, there were 27 denied claims that did not result in a PA request. Of these claims, 12 of them (44%) were associated with an unfunded condition (acne, rosacea, and Hidradenitis suppurativa). All of these claims were for extended therapy (>29 days). However, the remaining denied

DRAFT

claims (56%) were associated with a funded condition, including sinusitis, skin or soft tissue infection, bite wound, prostatitis, pneumonia). Only 2 of these claims were for treatment beyond 14 days.

Table 1: Outcome of Paid and Denied Claims from 7/1/2016 to 9/30/2016

	Initially Paid		Paid Within 30 days		Paid Within 31-90 Days		Another Drug in PDL Class Paid Within 30 days		Another Drug in PDL Class Paid Within 31-90 days		No Drugs Within PDL Class Paid Within 90 Days		Total #	Total %
Row Labels	#	%	#	%	#	%	#	%	#	%	#	%		
Tetracyclines, Oral	300	47%	39	6%	0	0%	37	6%	1	0%	260	41%	637	100%
Y	286	66%	19	4%	0	0%	9	2%	1	0%	121	28%	436	100%
DOXYCYCLINE HYCLATE	160	68%	8	3%	0	0%	6	3%	1	0%	61	26%	236	100%
DOXYCYCLINE MONOHYDRATE	122	65%	10	5%	0	0%	3	2%	0	0%	53	28%	188	100%
TETRACYCLINE HCL	4	33%	1	8%	0	0%	0	0%	0	0%	7	58%	12	100%
N	14	7%	20	10%	0	0%	28	14%	0	0%	139	69%	201	100%
DEMECLOCYCLINE HCL	0	0%	0	0%	0	0%	0	0%	0	0%	1	100%	1	100%
DOXYCYCLINE HYCLATE	0	0%	0	0%	0	0%	2	40%	0	0%	3	60%	5	100%
DOXYCYCLINE IR-DR	0	0%	1	33%	0	0%	0	0%	0	0%	2	67%	3	100%
DOXYCYCLINE MONOHYDRATE	6	5%	11	10%	0	0%	25	23%	0	0%	69	62%	111	100%
MINOCYCLINE HCL	8	10%	8	10%	0	0%	1	1%	0	0%	62	78%	79	100%
ORACEA	0	0%	0	0%	0	0%	0	0%	0	0%	1	100%	1	100%
SOLODYN	0	0%	0	0%	0	0%	0	0%	0	0%	1	100%	1	100%

DRAFT

Table 2: Denied Claims from 7/1/2016 to 9/30/2016

Row Labels	Enrolled in CCO		Lost Eligibility		Has Other Insurance		Indian Health Service Coverage		PA Approved		PA Denied		PA Not Requested		Total #	Total %
	#	%	#	%	#	%	#	%	#	%	#	%	#	%		
Tetracyclines, Oral	82	32%	32	12%	82	32%	11	4%	0	0%	8	3%	45	17%	260	100%
Y	42	35%	13	11%	28	23%	7	6%	0	0%	4	3%	27	22%	121	100%
DOXYCYCLINE HYCLATE	20	33%	5	8%	19	31%	0	0%	0	0%	0	0%	17	28%	61	100%
DOXYCYCLINE MONOHYDRATE	18	34%	8	15%	9	17%	7	13%	0	0%	2	4%	9	17%	53	100%
TETRACYCLINE HCL	4	57%	0	0%	0	0%	0	0%	0	0%	2	29%	1	14%	7	100%
N	40	29%	19	14%	54	39%	4	3%	0	0%	4	3%	18	13%	139	100%
DEMECLOCYCLINE HCL	0	0%	0	0%	1	100%	0	0%	0	0%	0	0%	0	0%	1	100%
DOXYCYCLINE HYCLATE	0	0%	1	33%	0	0%	0	0%	0	0%	0	0%	2	67%	3	100%
DOXYCYCLINE IR-DR	1	50%	0	0%	1	50%	0	0%	0	0%	0	0%	0	0%	2	100%
DOXYCYCLINE MONOHYDRATE	16	23%	11	16%	26	38%	4	6%	0	0%	1	1%	11	16%	69	100%
MINOCYCLINE HCL	23	37%	7	11%	24	39%	0	0%	0	0%	3	5%	5	8%	62	100%

DRAFT

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	CAPSULE	DOXYCYCLINE HYCLATE	DOXYCYCLINE HYCLATE	Y
ORAL	CAPSULE	MORGIDOX	DOXYCYCLINE HYCLATE	Y
ORAL	CAPSULE	VIBRAMYCIN	DOXYCYCLINE HYCLATE	Y
ORAL	TABLET	DOXYCYCLINE HYCLATE	DOXYCYCLINE HYCLATE	Y
ORAL	TABLET	DOXYCYCLINE HYCLATE	DOXYCYCLINE HYCLATE	Y
ORAL	SUSP RECON	DOXYCYCLINE MONOHYDRATE	DOXYCYCLINE MONOHYDRATE	Y
ORAL	SUSP RECON	VIBRAMYCIN	DOXYCYCLINE MONOHYDRATE	Y
ORAL	CAPSULE	DOXYCYCLINE MONOHYDRATE	DOXYCYCLINE MONOHYDRATE	Y
ORAL	CAPSULE	TETRACYCLINE HCL	TETRACYCLINE HCL	Y
ORAL	SYRUP	VIBRAMYCIN	DOXYCYCLINE CALCIUM	N
ORAL	TABLET DR	DORYX	DOXYCYCLINE HYCLATE	N
ORAL	TABLET DR	DOXYCYCLINE HYCLATE	DOXYCYCLINE HYCLATE	N
ORAL	CAP IR DR	DOXYCYCLINE IR-DR	DOXYCYCLINE MONOHYDRATE	N
ORAL	CAP IR DR	ORACEA	DOXYCYCLINE MONOHYDRATE	N
ORAL	CAPSULE	DOXYCYCLINE MONOHYDRATE	DOXYCYCLINE MONOHYDRATE	N
ORAL	TABLET	DOXYCYCLINE MONOHYDRATE	DOXYCYCLINE MONOHYDRATE	N
ORAL	TABLET	DEMECLOCYCLINE HCL	DEMECLOCYCLINE HCL	N
ORAL	CAPSULE	MINOCYCLINE HCL	MINOCYCLINE HCL	N
ORAL	TAB ER 24H	MINOCYCLINE HCL ER	MINOCYCLINE HCL	N
ORAL	TAB ER 24H	SOLODYN	MINOCYCLINE HCL	N
ORAL	TABLET	MINOCYCLINE HCL	MINOCYCLINE HCL	N

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Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to January Week 2 2017, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

# ▲	Searches	Results
1	tetracyclines.mp. or Tetracyclines/	3142
2	doxycycline.mp. or Doxycycline/	9726
3	minocycline.mp. or Minocycline/	5175
4	limit 3 to (english language and humans and yr="2015 -Current" and (controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or systematic reviews))	30
5	from 4 keep 19, 24-25	3

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