

LIST OF RECOMMENDED ANTIMICROBIAL RESTRICTIONS

Purpose of this document

The implementation of appropriate antimicrobial formulary restrictions is considered a core strategy of antimicrobial stewardship in Australian hospitals.¹ This *List of Recommended Antimicrobial Restrictions* provides guidance to facilities that are implementing antimicrobial restriction and approval policies, with its content based on both existing lists and expert opinion. The list provides information on which antimicrobial agents are commonly restricted, the most commonly recommended extent or level of restriction, and standardised justifications for restriction of each agent.

The *List of Recommended Antimicrobial Restrictions* may be amended at local level by the facility or LHD committee that oversees antimicrobial stewardship. The Clinical Excellence Commission recognises that the level of resources available in NSW hospitals to support antimicrobial stewardship varies significantly, as does the range of antimicrobial agents kept and the types of infectious diseases treated. The availability of staff with expertise in the treatment of infectious diseases, and their capacity to provide guidance on antimicrobial use, may also affect the choice and extent of restrictions that are put in place at a local level.

Rationale for Restrictions

The case for implementing antimicrobial restrictions within a hospital formulary is very well-established.¹ An informed and consistent approach to restricting antimicrobial use has been shown to improve the quality of antimicrobial prescribing, reduce rates of emerging resistance and deliver a range of positive outcomes across many areas of patient care.¹

In terms of the rationale for restricting individual antimicrobial agents, recommendations are made based on patient safety, disease state complexity, risk of antimicrobial resistance, best practice prescribing and public health interests. Pharmacoeconomic considerations may also be taken into account, however expenditure should rarely be the sole factor involved in a recommendation for antimicrobial restriction.

Formulary Adjustments

Not all agents on the *List of Recommended Antimicrobial Restrictions* need to be kept on a hospital formulary. Adjustments to the formulary are to be made at the discretion of the facility or LHD committee that oversees antimicrobial stewardship and/or the Drug and Therapeutics Committee. Where adjustments have been made, information detailing of the rationale for change and a discussion of clinical impacts should be disseminated widely to all prescribers, pharmacists and nursing managers.

Types of Restriction

Expert Approval

Restrictions based on expert approval require a nominated expert to have input or involvement in the prescribing of the antimicrobial agent. Authorisation is usually sought from an infectious diseases physician, clinical microbiologist or a consultant of a particular specialty, as determined by the committee that oversees antimicrobial stewardship and/or the Drug and Therapeutics Committee. Restrictions based on expert approval are useful for antimicrobial agents used in particularly challenging or rare disease states, or for infections with multi-drug resistant organisms. The need to involve a nominated 'approver' however, can be labour-intensive, thus widespread use of restrictions requiring expert approval may not always be achievable in facilities with limited resources and support.

Criteria-based

Criteria-based restrictions outline conditions that must be met for an antimicrobial prescription to be automatically approved. These restrictions may specify approved use of an antimicrobial for a particular indication, clinical scenario or duration of therapy, and may revert to an expert approval restriction should the criteria not be met. Restrictive criteria are determined by a committee that oversees antimicrobial stewardship and/or the Drug and Therapeutics Committee. Criteria-based restrictions are useful for improving the appropriateness of antimicrobial prescribing, but at times may be challenging to monitor and enforce.

Levels of Restriction

Antimicrobial restrictions are often categorised in a 'traffic-light system'. Whilst this is not an absolute requirement, such a system is recognised across many Australian healthcare facilities and it is generally considered to be a successful tool for educating prescribers about a local antimicrobial restriction policy.

RED - Highly Restricted

Most red antimicrobials require discussion with an infectious disease (ID) physician or clinical microbiologist (or a nominated medical officer) **prior to use**, however some restriction may be criteria-based where appropriate. Consideration must be given on how to manage requests for highly restricted antimicrobials in life-threatening and/or urgent situations 24 hours a day, 7 days a week.

ORANGE - Restricted

Orange antimicrobial agents are often subject to criteria-based restrictions. Many orange antimicrobials are restricted to use for selected indications or for a limited amount of time (e.g. 24 to 72 hours) prior to seeking approval from an ID physician or clinical microbiologist, or a nominated medical officer. These agents often require approval **after initiation** of therapy. Some agents may be classified as orange for specific indications and red for all other indications.

GREEN - Unrestricted

Green antimicrobial agents should be prescribed sensibly and appropriately, but have no specific restrictions on their use.

Restriction Details

Restriction details should be determined and reviewed by the committee that oversees antimicrobial stewardship and should be reflective of local resources and needs.

Prescribers, pharmacists and other clinical staff must have ready access to full restriction lists on every ward. Restriction details should be kept clear and succinct, and may separate antimicrobial agents based on product formulations and route of administration where appropriate.

Important Safety Considerations

The implementation of antimicrobial restriction policy should not prevent timely access to antimicrobials for life-saving conditions. Care must be taken to ensure patients

receive appropriate therapy at scheduled administration times, particularly if restricted agents are not available in ward imprest rooms or cupboards. If restricted antimicrobials are solely kept in the pharmacy department, consideration must be given to how these antimicrobials can be accessed outside of pharmacy hours. Staff involved in dispensing or distributing restricted antimicrobials should receive appropriate guidance on the degree to which restrictions are enforced. Policies and procedures may allow access to the 'first dose' or 'first 24 hours' of therapy while awaiting review and approval.

Bioavailability of Oral Antimicrobials

Antimicrobial agents with a high oral bioavailability will usually afford excellent penetration of drug into the systemic circulation. In most cases, intravenous administration of such agents offers little to no significant advantage over oral administration. The table below provides bioavailability information of agents for which oral administration is usually sufficient.

Antimicrobial	Oral Bioavailability ^{2,3,4}
Clindamycin	90%
Fluconazole	>90%
Metronidazole	100%
Ciprofloxacin	70-80%
Trimethoprim + Sulfamethoxazole	>85%

Antimicrobial stewardship strategies should aim to optimise antimicrobial use whilst still accounting for those scenarios in which oral administration may not be suitable (such as in patients who are nil by mouth, have absorption or tolerability issues, or who have infections of life-threatening severity). Where a higher level of restriction is placed on an intravenous agent compared to the oral equivalent, guidelines on IV to oral switch may be useful.

Conflict resolution

Policies and procedures for antimicrobial restrictions should clearly outline what action should be taken in the event that there is disagreement between the treating clinician (or antimicrobial prescriber) and the clinician granting approval for a restricted antimicrobial agent (or antimicrobial approver). This is best determined by the committee that oversees antimicrobial stewardship and/or the Drug and Therapeutics Committee, in liaison with the facility/LHD executive.

Off-label Use

Antimicrobial products are occasionally prescribed 'off-label' for non-infective indications. In these scenarios, permission to access a restricted agent should be sought from the Drug & Therapeutics Committee rather than a nominated infectious diseases expert or antimicrobial stewardship team.

Need more advice regarding antimicrobial restrictions and approvals?

Please feel free to contact the CEC Quality Use of Antimicrobials in Healthcare (QUAH) program if you have any questions:

CEC-AMS@health.nsw.gov.au

References & Acknowledgements

1. Duguid M and Cruickshank M (eds). *Antimicrobial Stewardship in Australian Hospitals*. Sydney : Australian Commission on Safety and Quality in Health Care, 2010.
2. Micromedex 2.0 DRUGDEX® System. Truven Health Analytics, Michigan, USA. Available through: CIAP <http://www.ciap.health.nsw.gov.au> [accessed 20 Jan 2017].
3. Burke A (2006). Oral Antibiotic Therapy of Serious Systemic Infections. *Med Clin N Am*. 90; 1197-1222
4. Sanford Guide (2016). Antimicrobial Therapy, Inc. Mobile application software [accessed 20 Jan 2017].
5. Australian Medicines Handbook 2017 (online). Adelaide: Australian Medicines Handbook Pty Ltd; 2017 Jan. Available from: <http://www.amh.net.au> [accessed 20 Jan 2017].

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List of Recommended Antimicrobial Restrictions

A component of the QUAH Antimicrobial Stewardship Toolkit

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Table 1: SYSTEMIC ANTIMICROBIAL AGENTS

This list contains agents given by the parenteral and oral route only, except where specified. It includes antibacterials, antifungals, antivirals (excluding those for chronic infections such as HIV, and Hepatitis B and C), antiprotozoals and anthelmintics. It excludes antimicrobials not registered for use in Australia.

ANTIMICROBIAL (Systemic)	RESTRICTION LEVEL	RATIONALE*
Aciclovir (oral)	GREEN	N/A
Aciclovir (injectable)	ORANGE	1,2
Albendazole	ORANGE	1
Amikacin	RED	3,4
Amoxicillin	GREEN	N/A
Amoxicillin with clavulanic acid	GREEN ^	N/A
Amphotericin (all IV formulations)	RED	4
Ampicillin	GREEN	N/A
Anidulafungin	RED	1,4
Artemether + lumefantrine	ORANGE	1
Atovaquone	ORANGE	1
Atovaquone + proguanil	ORANGE	1
Azithromycin (oral)	ORANGE	3,6,7
Azithromycin (inj)	RED	2
Aztreonam	RED	4,8
Benzathine (benzyl)penicillin	GREEN	N/A
Benzylpenicillin	GREEN	N/A
Capreomycin	RED	1
Caspofungin	RED	1,4
Cefaclor	GREEN	N/A
Cefalotin	GREEN	N/A
Cefepime	ORANGE	3,9
Cefotaxime	ORANGE	7,9
Cefoxitin	ORANGE	4
Ceftaroline	RED	5

ANTIMICROBIAL (Systemic)	RESTRICTION LEVEL	RATIONALE*
Ceftazidime	ORANGE	3,9
Ceftolozane with tazobactam	RED	4,5
Ceftriaxone	ORANGE	7,9
Cefuroxime	GREEN	N/A
Cephalexin	GREEN	N/A
Cephazolin	GREEN	N/A
Chloroquine	ORANGE	1
Cidofovir	RED	1,4
Ciprofloxacin (oral)	ORANGE	7,9
Ciprofloxacin (inj)	RED	2
Clarithromycin	ORANGE	10,11
Clindamycin	ORANGE	7
Colistin	RED	1,4
Cycloserine	RED	1
Dapsone	RED	1,4
Daptomycin	RED	1
Dicloxacillin	GREEN	N/A
Doxycycline	GREEN	N/A
Ertapenem	RED	6,9
Erythromycin	GREEN	N/A
Ethambutol	ORANGE	12
Famciclovir	ORANGE	6
Fidaxomicin	RED	1,5
Flucloxacillin	GREEN	N/A
Fluconazole	ORANGE	7
Flucytosine	RED	1,4
Foscarnet	RED	1,4

^ Some facilities may classify injectable forms of this antimicrobial agent as ORANGE

ANTIMICROBIAL (Systemic)	RESTRICTION LEVEL	RATIONALE*
Ganciclovir	RED	1
Gentamicin (up to 48 hrs)	ORANGE	13
Gentamicin (after 48 hrs)	RED	13
Griseofulvin	GREEN	N/A
Hexamine hippurate	GREEN	N/A
Imipenem	RED	9,10
Isoniazid	ORANGE	12
Itraconazole	ORANGE	1
Ivermectin	ORANGE	1,4
Lincomycin	ORANGE	6,7
Linezolid	RED	1,4
Mebendazole	GREEN	N/A
Mefloquine	ORANGE	4,7
Meropenem	RED	9
Metronidazole (oral)	GREEN	N/A
Metronidazole (inj)	ORANGE	2
Micafungin	RED	1,4,5
Minocycline	GREEN	N/A
Moxifloxacin (oral)	ORANGE	3,9
Moxifloxacin (inj)	RED	2
Neomycin	ORANGE	13
Nitrofurantoin	GREEN	N/A
Norfloxacin	ORANGE	7
Nystatin	GREEN	N/A
Oseltamivir	ORANGE	7
Palivizumab	RED	14
Pentamidine	RED	1,4
Phenoxymethylpenicillin	GREEN	N/A
Piperacillin with tazobactam	ORANGE	3,7,9
Posaconazole	RED	1,2
Praziquantel	ORANGE	1,7

ANTIMICROBIAL (Systemic)	RESTRICTION LEVEL	RATIONALE*
Primaquine	RED	4,7
Procaine penicillin	GREEN	N/A
Pyrantel	GREEN	N/A
Pyrazinamide	ORANGE	12
Pyrimethamine	RED	1,7
Quinine	RED	4
Rifabutin	RED	1,4
Rifampicin (used in combination for TB or MRSA)	ORANGE	11,12,15
Rifampicin (all other indications)	RED	11,12,15
Rifaximin	ORANGE	4,5,17
Roxithromycin	GREEN	N/A
Sodium fusidate (used in combination for MRSA)	ORANGE	15
Sodium fusidate (all other indications)	RED	15
Streptomycin	RED	1,4
Sulfadiazine	RED	1,4
Teicoplanin	RED	4,6
Terbinafine	GREEN	N/A
Ticarcillin with clavulanic acid	ORANGE	3,7,9
Tigecycline	RED	1,4
Tinidazole	GREEN	N/A
Tobramycin	ORANGE	6,13
Trimethoprim	GREEN	N/A
Trimethoprim + sulfamethoxazole	GREEN+	N/A
Valaciclovir	ORANGE	6
Valganciclovir	RED	1
Vancomycin	ORANGE	15
Voriconazole	RED	1

* Some facilities may classify injectable forms of this antimicrobial agent as RED

Table 2: TOPICAL ANTIBACTERIAL AGENTS

This list contains antibacterial agents given by the topical route only. It excludes topical antifungal and antiviral agents which are not commonly subject to restriction, and antibacterials which are not registered for topical use in Australia.

ANTIMICROBIAL (Topical)	RESTRICTION LEVEL	RATIONALE*
Ciprofloxacin	ORANGE	16
Chloramphenicol (ear, eye)	GREEN	N/A
Chloramphenicol (all other topical use)	ORANGE	17
Clindamycin	ORANGE	16
Erythromycin	ORANGE	16
Framycetin (eye, ear)	GREEN	N/A
Framycetin (all other topical use)	ORANGE	17
Gentamicin (eye)	GREEN	N/A
Gentamicin (all other topical use)	ORANGE	17
Gramicidin (ear)	GREEN	N/A
Gramicidin (all other topical use)	ORANGE	17
Metronidazole	ORANGE	16
Mupirocin	ORANGE	16
Neomycin (ear)	GREEN	N/A
Neomycin (all other topical use)	ORANGE	17
Ofloxacin	ORANGE	16
Propamidine (eye)	GREEN	N/A
Propamidine (all other topical use)	ORANGE	17
Silver sulfadiazine	ORANGE	16
Sodium fusidate	ORANGE	16
Tobramycin (eye)	GREEN	N/A
Tobramycin (all other topical use)	ORANGE	17

***RATIONALE(S) FOR RESTRICTION**

- Used in the management of complex, resistant or emerging infectious diseases; seek expert advice from an ID physician and/or medical microbiologist
- Oral dose form preferred where possible (less expensive)
- Other agents within the same class preferred (narrower spectrum)
- Rarely indicated as a first line agent; see expert advice from an ID physician and/or medical microbiologist
- New antimicrobial agent; seek expert advice from an ID physician and/or medical microbiologist
- Other agents within the same class preferred where possible (less expensive)
- Potential for overuse in common infections (when other agents may be more appropriate)
- Reserve use for patients with severe penicillin hypersensitivity; for other indications seek expert advice
- Broad-spectrum agent; linked with emergence of multi-resistant Gram negative organisms
- Other agents within the same class preferred as they have less toxicity
- Increased potential to induce antimicrobial resistance
- First-line agent for pulmonary tuberculosis (TB) infection; patients and close contacts need to be managed by clinicians with appropriate training and experience
- Should be switched to a less toxic agent after 48 hours
- Generally restricted to use in high risk patients in specialised settings
- Reserve use for methicillin-resistant *Staph. aureus* (MRSA) or suspected MRSA infections; for other indications seek expert advice
- When used topically, associated with development of antimicrobial resistance and topical sensitisation⁴
- Potential for off-label use in this setting