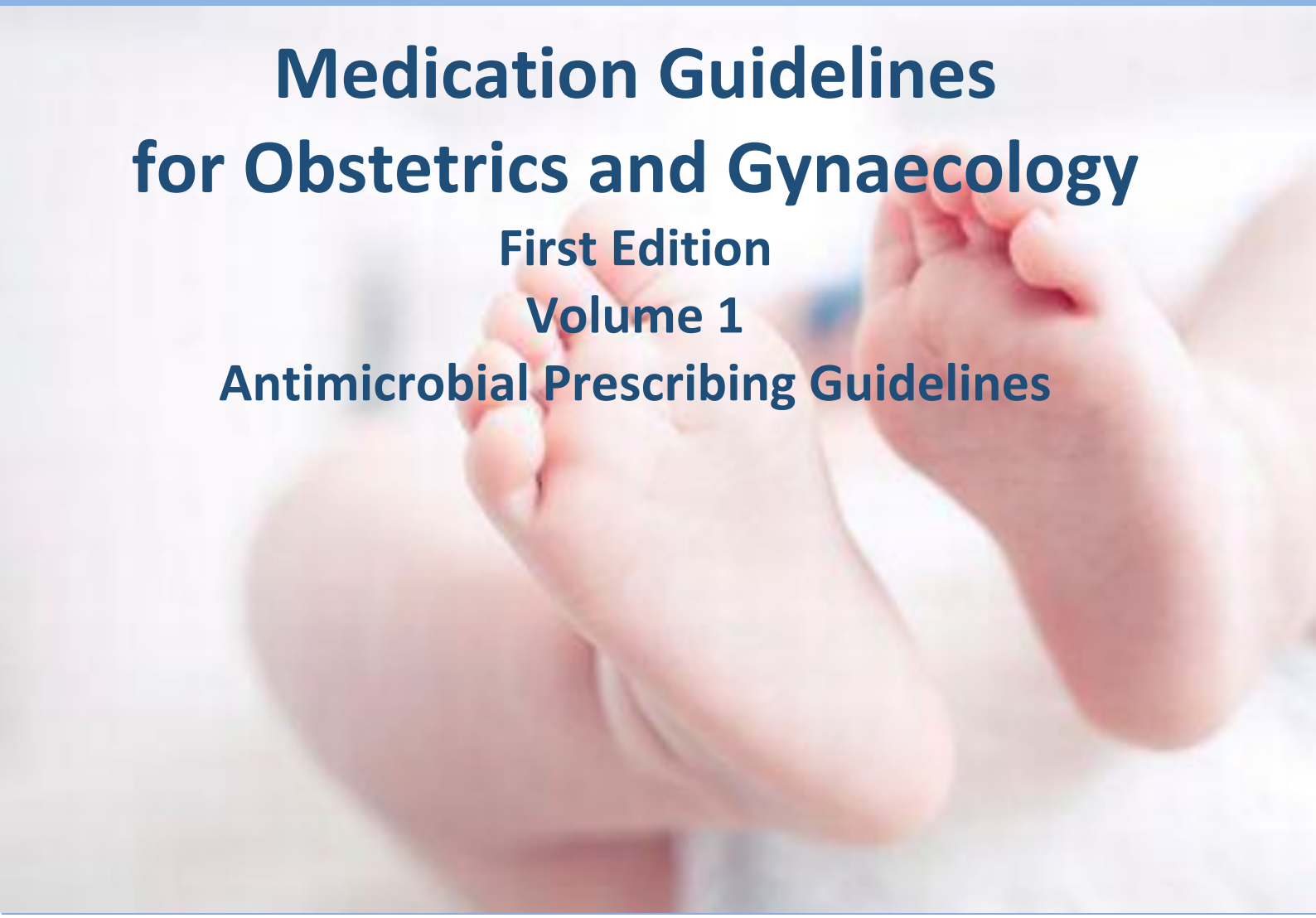

Medication Guidelines for Obstetrics and Gynaecology

First Edition

Volume 1

Antimicrobial Prescribing Guidelines

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Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

OBSTETRICS AND GYNAECOLOGY

Preface

In Ireland, infection complicates about one in three pregnancies (Downey et al, personal communication). Some are diagnosed and treated in a hospital setting but as overnight bed stays shorten, many are managed in a community setting. The management of infection in the obstetric patient brings with it the same challenges as outside pregnancy, for example, the choice of the most appropriate antibiotic, drug allergies, optimisation of the route and dose of the drug prescribed, the development of antibiotic resistance and the financial cost.

However, pregnancy poses its own specific challenges in the management of infection, for example, modulation of the maternal immune system, alterations in pharmacokinetics, the risk of teratogenesis, physiological changes as pregnancy advances, compatibility with breastfeeding. The breaching of physical barriers to organisms increases vulnerability peripartum, which is more likely as interventions such as Caesarean section increase. The increasing mobility of young women with migration and more exotic holidaying increases the risk of infection due to new or emerging organisms.

The clinical spectrum of infection varies widely from asymptomatic urinary tract infections to chorioamnionitis which may lead quickly to a critical maternal sepsis that threatens the life and health of the woman and her baby. The clinical presentation may be florid and immediately obvious from the history and examinations or, may be subtle and difficult to diagnose even with sophisticated investigations. Modern medicine has witnessed major advances in our knowledge of the prevention and treatment of infection and its adverse clinical outcomes, including sepsis. There have been advances in microbiological surveillance and in therapeutics. We also know that worldwide, even in well-resourced countries there are wide variations in clinical outcomes in both hospital and community settings which may be attributable, in part, to variations in treatment including drug usage.

The purpose of this First Edition of a National Medications Programme (Volume 1) for antimicrobial prescribing in pregnancy is to improve the quality of care for all women and their offspring attending our maternity services whatever the setting. It follows the development of a number of clinical practice guidelines for infections and pregnancy by the Clinical Programme in Obstetrics and Gynaecology, and the recent appointment of antibiotic pharmacists for the maternity services in all six Hospital Groups in the country. It also addresses one of the key priorities identified by the National Implementation Group which supports the implementation of the HIQA Patient Safety Investigation report into services at University Hospital Galway.

This First Edition will be disseminated widely for implementation using a variety of communication channels. We anticipate that as our knowledge grows, as patterns of infection evolve, as diagnostic techniques improve etc that this Edition will have to be frequently revised. We would also welcome ongoing feedback on this repository from frontline staff in the future.

We thank all our colleagues around the country who contributed both individually and collectively and who generously shared their expertise in this national endeavour. We thank Gethin White and Aoife Lawton from the Library in Dr Steeven's Hospital for their academic resourcing, and Caroline Plascott and Martin McNicholl for their strong administrative support. We would also like to thank Ms. Michelle O'Connor for her invaluable help in formatting this document. Finally, we

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1 Abbreviations

ACOG	American College of Obstetricians and Gynecologists
BCG	Bacillus Calmette Guérin (tuberculosis)
BNF	British National Formulary
BSACI	British Society for Allergy and Clinical Immunology
CG	Cockcroft and Gault Formula
CKD	Chronic Kidney Disease
CRE	Carbapenem Resistant Enterobacteriaceae
eGFR	Estimated Glomerular Filtration Rate
ESBL	Extended Spectrum β-lactamases
FDA	Food and Drug Administration
GDG	Guideline Developing Group
GFR	Glomerular Filtration Rate
HBV	Hepatitis B Vaccine
HPRA	Health Products Regulatory Authority
HPV	Human Papillomavirus
HSE	Health Service Executive
HSV	Herpes Simplex Virus
IDSA	Infectious Disease Society of America
IUGR	Intrauterine Growth Restriction
IVIg	Intravenous Immunoglobulin
KDOQI	UK Renal Association Kidney Disease Outcomes Quality Initiative
MAOI	Monoamine Oxidase Inhibitor
MDRO	Multi-drug Resistant Organisms
MMR	Measles, Mumps & Rubella
MRSA	Methicillin Resistant *Staphylococcus aureus*
NEC	Neonatal Necrotising Enterocolitis
NIAC	National Immunisation Advisory Committee
NICE	UK National Institute for Health and Clinical Excellence
NMIC	National Medicines Information Centre
OPAT	Out-patient Antimicrobial Therapy
PPROM	Preterm Premature Rupture of Membranes
PPS	Point Prevalence Survey
RCOG	Royal College of Obstetrics and Gynaecology
RCPI	Royal College of Physicians in Ireland
SPC	Summary of Product Characteristics
TDM	Therapeutic Drug Monitoring
UKDILAS	UK Drugs in Lactation Advisory Service
UTI	Urinary Tract Infection
Varicella	Chicken Pox
VRE	Vancomycin Resistant Enterococcus

2 Introduction

2.1 Purpose

The purpose of these guidelines is to have a single reference document in which different options for the treatment of infections in pregnancy are presented, with some detail also regarding use of antimicrobials in lactation and teratogenicity risk.

These guidelines are not to replace local guidelines which currently exist in the maternity units, but to support the development of local guidelines in each unit and to act as a reference document for local specialists. In individual cases a healthcare professional may, after careful consideration, decide not to follow the guideline if it is deemed to be in the best interests of the woman or her baby.

The guidelines were developed in response to priorities set down by a National Implementation Group, which was established in late 2013 following the publication of the HSE Investigation of Incident 50278 in June 2013, and the subsequent publication of the HIQA Investigation into the safety, quality and standards of services provided by the HSE to patients, including pregnant women, at risk of clinical deterioration, including those provided in University Hospital Galway, and as reflected in the care and treatment provided to Savita Halappanavaar. Priority number 5 refers to the development of a National Medication Programme for obstetrics and gynaecology. This First Edition of Volume 1 of the National Medication Programme, comprising national antimicrobial guidelines, will be followed by Volume 2 which will provide further national guidance for prescribing medications and treatments in pregnancy.

2.2 Methodology

Medline, EMBASE. NICE and Cochrane Database of Systematic Reviews were searched using terms relating to toxicity in pregnancy and breastfeeding of the different indications covered by these guidelines and the drugs used to treat them. The references of the literature that resulted from these searched was analysed also.

Searches were limited to humans and restricted to the titles of English language articles published between 2011 – current, the references of these articles were then searched for relevant publications also.

Relevant meta-analyses, systematic reviews, intervention and observational studies were reviewed. Guidelines reviewed include national guidelines from Australia, Canada, Ireland, New Zealand, Northern Ireland, UK and USA. For full list of guidelines reviewed, see the references at end of document.

The principal guideline developers were Ms. Mairead McGuire, Dr Richard Drew and Professor Michael Turner. The strong administrative support provided by Ms. Caroline Plascott and Mr. Martin McNicholl is also acknowledged as is the invaluable formatting guidance given by Ms. Michelle O'Connor.

3 Treatment Monographs for Infections in Pregnancy

3.1 Introduction

The following treatment monographs are meant as guidelines for prescribers, they do not replace clinical judgement but augment it. These prescribing guidelines have been developed after review of national and international guidelines and current practice, expert opinion, clinical consensus and published evidence where it exists.

Each maternity unit should have their own clinical guidelines specific to that unit. These guidelines are not to replace local guidelines which currently exist in the maternity units, but to support the further development of guidelines in each unit and to act as a reference document for local specialists.

We would particularly like to acknowledge the Maternity units around the country who agreed to share their prescribing guidelines as part of the review process. Before prescribing antimicrobials for a pregnant women, clinicians should also consider the following:

- Local antimicrobial sensitivities and resistance data, especially the rate of erythromycin resistance in Group B Streptococcus isolates at the institution
- Previous antimicrobial treatment the woman has been prescribed for the current and previous infections during this pregnancy
- The allergy status of the woman
- Exposure of the fetus to the prescribed antimicrobial and its possible teratogenicity
- Concurrent medication that the woman is taking
- The stage of pregnancy
- Concurrent morbidities

It is important to recognise that antibiotics should be administered during pregnancy at the upper end of their suggested dosing ranges, as pregnant women have an increased GFR and volume of distribution ranges are higher (Harbison et al., 2015).

3.2 Treatment monographs: Antenatal Infections

Antenatal Infection	No penicillin allergy	Non-immediate penicillin allergy	Severe or immediate penicillin allergy	Notes
Urinary tract **Asymptomatic bacteriuria and lower UTI (E.coli, Enterococcus, GBS)**	Nitrofurantoin 50-100mg QDS PO Or Cephalexin 500mg BD-TDS PO	Nitrofurantoin 50-100mg QDS PO Or Cephalexin 500mg BD-TDS PO	Nitrofurantoin 50-100mg QDS PO	A repeat urine should be sent after treatment to confirm clearance of the organism.
Pyelonephritis **(E.coli, GBS, Klebsiella)**	Option 1 Ceftriaxone 1-2g OD IV Or Cefotaxime 1g TDS IV (Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose of in 3 divided doses may be added if woman is systemically unwell) Option 2 Co-amoxiclav 1.2g TDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose of in 3 divided doses	Ceftriaxone 1-2g OD IV Or Cefotaxime 1g TDS IV (Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose of in 3 divided doses may be added)	Clindamycin 900mg TDS Or Vancomycin 15mg/kg BD (max 2g/dose) depending on GBS susceptibility AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose of in 3 divided doses	Oral switch should be considered once the woman is 48 hours afebrile and there is a suitable oral alternative based on antimicrobial susceptibility test results In the post-partum setting when the woman is not breastfeeding, Ciprofloxacin 750mg BD PO may also be considered. National Guideline publication pending

Antenatal Infection	No penicillin allergy	Non-immediate penicillin allergy	Severe or immediate penicillin allergy	Notes
Genital Tract **Chorioamnionitis (including septic miscarriage) (E.coli, GBS, Group A Streptococcus, Klebsiella)**	Option 1: Co-amoxiclav 1.2g TDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose or in 3 divided doses Option 2: Amoxicillin 1g QDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose or in 3 divided doses AND Metronidazole 500mg TDS IV Option 3: Benzylpenicillin 2.4g QDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose of in 3 divided doses AND Metronidazole 500mg TDS IV	Option 1: Ceftriaxone 1-2g OD IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose or in 3 divided doses AND Metronidazole 500mg TDS IV (Note that this regimen has no Listeria cover. If specific Listeria cover is required then add Vancomycin) Option 2: Clindamycin 900mg TDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose of in 3 divided doses	Option 1: Clindamycin 900mg TDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose of in 3 divided doses Option 2: Vancomycin 15mg/kg BD (max 2g/dose) AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose or in 3 divided doses AND Metronidazole 500mg TDS IV The choice between option 1 and 2 depends on the susceptibility of Group B Streptococcus to clindamycin	It is important that microbiological specimens (e.g. blood culture, high vaginal swab) are taken as soon as possible and sent to the laboratory for analysis.
Listeriosis	Amoxicillin 2g every four hours IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose or in 3 divided doses	Vancomycin 15mg/kg BD (max 2g/dose) AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose or in 3 divided doses	Vancomycin 15mg/kg BD (max 2g/dose) AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose or in 3 divided doses	This is a notifiable disease. All cases of invasive Listeria should be discussed with the microbiologist on duty and Public Health should be informed

3.3 Treatment monographs: Antenatal Infections - Sepsis

Antenatal Infection	No penicillin allergy	Non-immediate penicillin allergy	Severe or immediate penicillin allergy	Notes
Sepsis **(no identifiable source)**	Option 1: Co-amoxiclav 1.2g TDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose or in 3 divided doses Option 2: Any one of • Amoxicillin 1g QDS IV • Benzylpenicillin 2.4g QDS IV • Cefuroxime 1.5g QDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose of in 3 divided doses AND Metronidazole 500mg TDS IV	Option 1: Clindamycin 900mg TDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose of in 3 divided doses Option 2: Cefuroxime 1.5g QDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose of in 3 divided doses AND Metronidazole 500mg TDS IV	Option 1: Clindamycin 900mg TDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose of in 3 divided doses Option 2: Vancomycin 15mg/kg BD (max 2g/dose) AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose of in 3 divided doses AND Metronidazole 500mg TDS IV The choice between option 1 and 2 depends on the susceptibility of Group B Streptococcus to clindamycin	It is important that microbiological specimens (e.g. blood culture, high vaginal swab) are taken as soon as possible and sent to the laboratory for analysis. It is important that the source of the sepsis is identified quickly and the source of the sepsis is controlled The empirical antimicrobial regimen should be rationalised once cultures are available and the source of the sepsis has been identified.
Sepsis (Severe) **(e.g. septic shock refractory to initial resuscitation)**	Meropenem 1g TDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose or in 3 divided doses AND Clindamycin 1.2g QDS IV	Vancomycin 15mg/kg BD (max 2g/dose) AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose or in 3 divided doses AND Clindamycin 1.2g QDS IV Cefotaxime 2g QDS IV may also be added to improve Gram-negative cover	Vancomycin 15mg/kg BD (max 2g/dose) AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose or in 3 divided doses AND Clindamycin 1.2g QDS IV Ciprofloxacin 500mg BD IV may also be added to improve Gram-negative cover	If using Vancomycin, consider giving a loading dose of 25mg/kg (max 2g/dose) initially If MRSA is present, always give vancomycin in addition to the other antimicrobials. Senior obstetric and anaesthetic staff should be involved in these cases.

3.4 Treatment monographs: Antenatal Infections-Intrapartum

Antenatal Infection	No penicillin allergy	Non-immediate penicillin allergy	Severe or immediate penicillin allergy	Notes
Intrapartum pyrexia	Option 1: Benzylpenicillin 3g stat then 2.4g QDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose or in 3 divided doses AND Metronidazole 500mg TDS IV Option 2: Cefuroxime 1.5g QDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose of in 3 divided doses AND Metronidazole 500mg TDS IV Option 3: Co-amoxiclav 1.2g TDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose or in 3 divided doses	Option 1: Cefuroxime 1.5g QDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose of in 3 divided doses AND Metronidazole 500mg TDS IV Option 2: Clindamycin 900mg TDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose of in 3 divided doses Option 3: Vancomycin 15mg/kg BD (max 2g/dose) depending on GBS susceptibility AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose of in 3 divided doses AND Metronidazole 500mg TDS IV The choice between option 2 and 3 depends on the susceptibility of Group B Streptococcus to clindamycin	Option 1: Clindamycin 900mg TDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose of in 3 divided doses Option 2: Vancomycin 15mg/kg BD (max 2g/dose) AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose or in 3 divided doses AND Metronidazole 500mg TDS IV The choice between option 1 and 2 depends on the susceptibility of Group B Streptococcus to clindamycin	It is important that the susceptibility of any previously grown Group B Streptococcus is checked prior to choosing the antimicrobial regimen. The neonatal team should be informed of cases of intrapartum pyrexia so that they can assess the baby. Institutions should monitor their rate of erythromycin/clindamycin resistance amongst Group B Streptococcal isolates to determine if it is reasonable to use clindamycin empirically.

3.5 Treatment monographs: Intrapartum Antimicrobial Prophylaxis and Preterm Premature Rupture of Membranes

Prophylaxis	No penicillin allergy	Non-immediate penicillin allergy	Severe or immediate penicillin allergy	Notes
Intrapartum antimicrobial prophylaxis for the reduction of early-onset invasive group B Streptococcal disease in the neonate	Option 1: Benzylpenicillin 3g stat then 1.5-1.8g every four hours IV	Option 1: Cefuroxime 1.5g QDS IV Option 2: Clindamycin 900mg TDS IV Option 3: Vancomycin 15mg/kg BD (max 2g/dose) The choice between option 2 and 3 depends on the susceptibility of Group B Streptococcus to clindamycin	Option 1: Clindamycin 900mg TDS IV Option 2: Vancomycin 15mg/kg BD (max 2g/dose) depending on GBS susceptibility The choice between option 1 and 2 depends on the susceptibility of Group B Streptococcus to clindamycin	If the mother herself is septic or pyrexial this section is not suitable. See section on intrapartum pyrexia or chorioamnionitis. The treatment should continue until the woman has delivered. For advice regarding which women require intrapartum prophylaxis see local guidelines.
Preterm-premature rupture of the membranes	Erythromycin 250-500mg QDS PO Or Clarithromycin 500mg OD PO (Klacid LA ®)	Erythromycin 250-500mg QDS PO Or Clarithromycin 500mg OD PO (Klacid LA ®)	Erythromycin 250-500mg QDS PO Or Clarithromycin 500mg OD PO (Klacid LA ®)	This should only be given if the woman is ≥ 20 weeks gestation. The duration of treatment should be 10 days.

3.6 Treatment monographs: Post-partum Infections

Postnatal Infection	No penicillin allergy	Non-immediate penicillin allergy	Severe or immediate penicillin allergy	Notes
Infective mastitis	Flucloxacillin 500mg -1g QDS PO	Cephalexin 500mg TDS PO	Clindamycin 300-450mg QDS PO	The woman should be encouraged to continue to breastfeed
Severe mastitis with suspected breast abscess	Flucloxacillin 1-2g QDS IV AND Clindamycin 450mg QDS PO	Option 1: Cefuroxime 1.5g QDS IV AND Clindamycin 450mg QDS PO Option 2: Clindamycin 900mg TDS IV	Clindamycin 900mg TDS IV For women with known clindamycin resistant S.aureus or if the woman is systemically unwell consider adding Vancomycin 15mg/kg BD IV (max 2g/dose)	If the woman is colonised with MRSA or thought to be at high risk (e.g. healthcare professional), then discuss with Microbiology
Endometritis (mild) **Perineal mild**	Co-amoxiclav 625mg TDS PO	Cephalexin 500mg TDS PO AND Metronidazole 400mg TDS PO	Clindamycin 300-450mg QDS PO	
Endometritis (severe) **OR** **Perineal Severe** **(This includes women with retained products of conception who present with sepsis)**	Option 1: Co-amoxiclav 1.2g TDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose or in 3 divided doses Option 2: Clindamycin 900mg TDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose or in 3 divided doses Option 3: Amoxicillin 1g TDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose or in 3 divided doses AND Metronidazole 500mg TDS IV	Option 1: Cefuroxime 1.5g QDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose or in 3 divided doses AND Metronidazole 500mg TDS IV Option 2: Clindamycin 900mg TDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose or in 3 divided doses Option 3: Vancomycin 15mg/kg BD (max 2g/dose) depending on GBS susceptibility AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose or in 3 divided doses AND Metronidazole 500mg TDS IV	Option 1: Clindamycin 900mg TDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose or in 3 divided doses Option 2: Vancomycin 15mg/kg BD (max 2g/dose) AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose or in 3 divided doses AND Metronidazole 500mg TDS IV The choice between option 1 and 2 depends on the susceptibility of Group B Streptococcus to clindamycin	See National Guideline: Management of Obstetric Anal Sphincter injury

Treatment monographs: Post-partum Infections continued

Postnatal infection	No penicillin allergy	Non-immediate penicillin allergy	Severe or immediate penicillin allergy	Notes
Caesarean section wound infection (superficial incisional)	Option 1: Flucloxacillin 500mg-1g QDS PO Option 2: Co-amoxiclav 625mg TDS PO	Option 1: Clindamycin 300-450mg QDS PO Option 2: Cephalexin 500mg TDS PO AND Metronidazole 400mg TDS PO	Clindamycin 300-450mg QDS PO	If the woman is colonised with MRSA or thought to be at high risk (e.g. healthcare professional), then discuss with Microbiology
Post C-section wound infection (deep incisional or organ space)	Option 1: Co-amoxiclav 1.2g TDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose of in 3 divided doses Option 2: Cefuroxime 1.5g QDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose of in 3 divided doses AND Metronidazole 500mg TDS IV	Option 1: Cefuroxime 1.5g QDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose of in 3 divided doses AND Metronidazole 500mg TDS IV Option 2: Clindamycin 900mg TDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose of in 3 divided doses	Clindamycin 900mg TDS IV AND Gentamicin 5mg/kg/day IV (max 480mg/day) in either one single dose of in 3 divided doses	If the woman is colonised with MRSA or thought to be at high risk (e.g. healthcare professional), then discuss with Microbiology Radiological imaging should be carried out as soon as possible when needed. When possible, intra-abdominal collections should be drained so as to achieve source control and obtain fluid for culture. For women requiring prolonged intravenous course of treatment, contact should be made with the local Out-Patient Antimicrobial Therapy (OPAT) team who may be able to facilitate administration of the drugs in the community.

3.7 Treatment monographs: Other Infections

Infection	No penicillin allergy	Non-immediate penicillin allergy	Severe or immediate penicillin allergy	Notes
Meningitis	Cefotaxime 2g QDS - 4 hourly IV (8-12g / day) Or Ceftriaxone 2g BD IV With or without Vancomycin 15mg/kg (max 2g/dose) BD IV **Note always add Amoxicillin 2g every 4 hours if patient is pregnant**	Cefotaxime 2g QDS - 4 hourly IV (8-12g /day) OR Ceftriaxone 2g BD IV With or without Vancomycin 15mg/kg (max 2g/dose) BD IV **Note always add Vancomycin if woman is pregnant**	Meropenem 2g TDS IV With or without Vancomycin 15mg/kg (max 2g/dose) BD IV **Note always add Vancomycin if woman is pregnant**	These cases **must** always be discussed with senior obstetric, anaesthetic and microbiology staff.
Lower respiratory tract infection (non-pneumonic)	Amoxicillin 500mg-1g TDS PO Or Clarithromycin 500mg BD PO (2nd and 3rd trimester) Or Erythromycin 250-500mg QDS PO (First trimester) Or Co-amoxiclav 625mg TDS PO (if influenza is suspected)	Clarithromycin 500mg BD PO (2nd and 3rd trimester) Or Erythromycin 250-500mg QDS PO (First trimester)	Clarithromycin 500mg BD PO (2nd and 3rd trimester) Or Erythromycin 250-500mg QDS PO (First trimester)	Erythromycin can be associated with nausea, vomiting and thus poor compliance. When possible consider using other alternatives.
Lower respiratory tract infection CAP (Community acquired pneumonia with moderate to severe symptoms)	Option 1 Co-amoxiclav 1.2g TDS IV AND Clarithromycin 500mg BD PO (note use erythromycin for clarithromycin in the first trimester) Option 2 Cefuroxime 1.5g QDS IV AND Clarithromycin 500mg BD PO (note use erythromycin for clarithromycin in the first trimester)	Cefuroxime 1.5g QDS IV AND Clarithromycin 500mg BD PO (note use erythromycin for clarithromycin in the first trimester)	Vancomycin 15mg/kg (max 2g/dose) BD IV AND Clarithromycin 500mg BD PO (note use erythromycin for clarithromycin in the first trimester)	

Infection	No penicillin allergy	Non-immediate penicillin allergy	Severe or immediate penicillin allergy	Notes
Peripheral venous catheter	Option 1: Flucloxacillin 500mg-1g QDS PO	Option 1: Clindamycin 300-450mg QDS PO Option 2: Cephalexin 500mg TDS PO	Clindamycin 300-450mg QDS PO	The peripheral venous catheter should always be removed if there are signs of infection present.
Bacterial tonsillitis	Phenoxymethylpenicillin 666mg QDS PO	Clarithromycin 500mg BD PO (2nd and 3rd trimester) Or Erythromycin 250-500mg QDS PO (First trimester)	Clarithromycin 500mg BD PO (2nd and 3rd trimester) Or Erythromycin 250-500mg QDS PO (First trimester)	
Meningococcal Prophylaxis **H. Influenzae B Prophylaxis** Prophylaxis for contact with meningococcal disease **or** ***Haemophilus influenzae*** **type B invasive disease**	Ceftriaxone 250mg IM stat dose (note intramuscular) Or Ciprofloxacin 500mg PO stat dose	Ceftriaxone 250mg IM stat dose (note intramuscular) Or Ciprofloxacin 500mg PO stat dose	Ciprofloxacin 500mg PO stat dose	This should be done in consultation with the local Public Health Specialists and Microbiology Consultant
Nipple and breast thrush	Topical miconazole should be given to the mother and baby. Systemic fluconazole should only be used in exceptional circumstances and under medical supervision for deep candida mastitis which is very rare. There is a significant risk of drug interactions and caution must be exercised when using fluconazole			
Uncomplicated Vulvovaginal Candidiasis	Non-pregnant patient: Clotrimazole 500mg vaginal pessary nocte stat dose Pregnant woman: Clotrimazole 200mg vaginal pessary for 3 or 6 nights, and clotrimazole cream may also be used topically			
Influenza	Oseltamavir 75mg BD should be given to women in the 2nd or 3rd trimester, as well as for women in the first trimester who have co-morbidities			Monitor women carefully for signs of bacterial super-infection (e.g. Group A Streptococcus)

4 Sexual Health and Sexually Transmitted Infections

Women who are pregnant can become infected with the same sexually-transmitted infections (STIs) as women who are not pregnant. Possible effects of STIs include miscarriage, premature-preterm rupture of membranes, premature birth, still births, neonatal death, babies being small for gestational age, low birth weight, multiple organ damage, neonatal infections e.g. of the eye and lung and congenital or vertical transmission.

The woman should be investigated for other STIs once one infection has been confirmed. Definite follow up of the woman should be arranged, and this can be done in line with local policies. The partner of the woman should be referred for assessment and this should be done urgently so as to prevent re-infection.

The recently published Centre for Disease Control and Prevention STI treatment guidelines 2015 may also be a useful resource for guidance on treatment of infection in this setting.

Disease	Organisms	Suggested regimen in pregnancy or the lactating woman	Suggested regimen in non-pregnant and non-lactating woman	Guidelines to consider	Notes
Pelvic Inflammatory disease	*Chlamydia trachomatis* *Neisseria gonorrhoeae*	**Lactating woman:** Ceftriaxone 500mg IM stat dose Followed by Erythromycin 500mg QDS PO AND Metronidazole 400mg BD x 14 days **Pregnant woman:** Ceftriaxone 2g OD IV, plus erythromycin 500mg QDS PO plus metronidazole 500mg BD IV. (Stop IV treatment if clinically appropriate after 24-48 hours)	**Mild disease:** Ceftriaxone 500mg IM stat dose plus doxycycline 100mg BD and metronidazole 400mg BD PO x 14 days **Severe disease:** Ceftriaxone 2g OD IV, plus doxycycline 100mg BD PO plus metronidazole 500mg BD IV.	UK national guideline for the management of PID 2011. BASHH	For women with severe disease consider changing to oral antibiotics once the woman is 24-48 hours afebrile An alternative regimen in penicillin allergy and pregnancy may be Clindamycin 900mg TDS IV with gentamicin 5mg/kg/day in a single dose or 3 divided doses Azithromycin may be used instead of erythromycin. See local guidelines for dosing
Genital Chlamydia	*Chlamydia trachomatis*	Azithromycin 1g stat dose PO	Azithromycin 1g stat dose PO	UK national guideline for the management of chlamydia 2006. BASHH	Ensure woman is referred to appropriate STI service

Disease	Organisms	Suggested regimen in pregnancy or the lactating woman	Suggested regimen in non-pregnant and non-lactating woman	Guidelines to consider	Notes
Gonorrhoea (cervix, urethra or rectum, pharynx)	*Neisseria gonorrhoeae*	Ceftriaxone 250-500mg stat dose IM with azithromycin 1g stat dose PO	Ceftriaxone 250-500mg stat dose IM with azithromycin 1g stat dose PO	UK national guideline for the management of gonorrhoea 2011. BASHH CDC STI guidelines 2015	Ensure woman is referred to appropriate STI service. ***Doses recommended*** CDC ceftriaxone250mg BASHH Ceftriaxone 500mg.
Trichomonas	*Trichomonas vaginalis*	Metronidazole 400mg-500mg BD PO x 7 days	Metronidazole 2g stat dose PO	Management of *Trichomonas vaginalis* 2014. BASHH	High dose metronidazole should be avoided in pregnancy, particularly in the first trimester. The sexual partner should be treated concurrently.
Bacterial vaginosis		Metronidazole 400mgBD PO x 7 days	Metronidazole 2g stat dose PO	UK national guideline on the management of Bacterial Vaginosis 2012. BASHH	
Genital Herpes - first presentation	HSV-1, HSV-2	Aciclovir 400mg TDS Or 200mg 5 times per day BASHH recommend 5 days treatment and CDC recommend 7-10 days treatment	Aciclovir 400mg TDS Or 200mg 5 times per day BASHH recommend 5 days treatment and CDC recommend 7-10 days treatment	Management of genital herpes in pregnancy. RCOG and BASHH 2014 UK National guideline for the management of anogenital herpes 2014. BASHH	Consider IV treatment if the lesions are very severe. See national Mother To Child Transmission guidelines for further advice, and for management of reactivation in pregnancy

5 Surgical Prophylaxis

5.1 Introduction

Infectious complications following obstetric surgical procedures are a significant source of morbidity and potential mortality. They include urinary tract infection, endometritis, wound infection, perineal infection and sepsis, which can lead to prolonged hospital stays and increased healthcare costs (van Schalkwyk and Van Eyk, 2010). The purpose of antibiotic prophylaxis in surgical procedures is not to sterilise the tissue but to reduce the colonisation pressure of microorganisms introduced at the time of operation to a level that the woman's immune system is able to overcome (Mangram et al., 1999). Prophylactic antibiotics have been proven effective in the reduction of post-operative infection and have been the standard of care in caesarean sections for decades (Carlson and Duff, 1990). In addition to antibiotic prophylaxis, it is essential to review all factors that affect infectious risk reduction in obstetrical care and comply with international best practice, for example effective antisepsis of both the woman and staff, maintenance of sterile surgical fields, assessment of sterilisation techniques, consistent infection control surveillance etc. The table below lists antimicrobial prophylaxis regimens for common obstetric surgical interventions.

5.2 Treatment monographs: Surgical Prophylaxis

Surgical prophylaxis	No penicillin allergy	Non-immediate Penicillin allergy	Immediate or Severe penicillin allergy	Duration of treatment
Caesarean section	Cefuroxime 1.5g stat dose IV Or Co-amoxiclav 1.2g stat dose IV	Cefuroxime 1.5g stat dose IV	Clindamycin 600-900mg IV stat dose and Gentamicin 5mg/kg (max 480mg/day) or 120mg IV stat dose	One dose. Give ideally before incision (60 to 15 minutes before) or in some cases at cord clamping.
Manual Removal of Placenta	Co-amoxiclav 1.2g stat dose IV	Clindamycin 600-900mg IV stat dose **and** Gentamicin 5mg/kg (max 480mg/day) or 120mg stat dose	Clindamycin 600-900mg IV stat dose and Gentamicin 5mg/kg (max 480mg/day) or 120mg stat dose	One dose.
Third or Fourth degree tear repair	Co-amoxiclav 1.2g IV	Clindamycin 600-900mg IV stat dose **and** Gentamicin 5mg/kg stat dose (max 480mg/day)	Clindamycin 600-900mg IV stat dose and Gentamicin 5mg/kg Stat dose (max 480mg/day)	24 hours

Note: If the surgery is prolonged (>3 hours) or there is severe haemorrhage (>1.5L blood loss), a second dose should be given 6-8 hours later in the case of co-amoxiclav, cefuroxime or the 120mg gentamicin dose.

6 Principles of Infection and Antimicrobial Use in Pregnancy

6.1 Infection in Pregnancy and the peripartum

In a recent Irish study, approximately 40% of pregnant women reported taking at least one medication, excluding folic acid, during pregnancy (Cleary et al., 2010). In a recent Swedish study of postpartum women, 10.3% reported at least one infectious episode and 7.5% had received antibiotics (Axelsson and Blomberg, 2014). Antimicrobials and antibacterial drugs in particular, are among the most commonly prescribed medications during pregnancy because treatment of infections is critical to the health of the mother and her fetus (Andrade et al., 2004).

The evidence indicates that pregnancy is associated with increased severity of some infectious diseases, such as influenza, malaria, Listeriosis, pneumonia and herpes simplex virus (HSV) infection (Sappenfield et al., 2013). Though HSV and hepatitis are rare in pregnancy, primary HSV infection in pregnancy confers a higher risk of dissemination and hepatitis especially in the third trimester (Sappenfield et al., 2013, Kourtis et al., 2014). The evidence is more limited for measles and varicella primary infection, though they may lead to a poor outcome for the developing fetus (Kourtis et al., 2014, Sappenfield et al., 2013).

Disease severity may also increase with advancing pregnancy. The influenza pandemic of 2009 provided a recent reminder that certain infections may disproportionately affect pregnant women particularly in the third trimester (Kourtis et al., 2014). Immunologic alterations that occur during pregnancy may help to explain the altered severity and /or susceptibility to infectious diseases during pregnancy (Kourtis et al., 2014).It should be noted that the threshold for diagnostic evaluation, as well as hospitalisation and treatment, may be lower for pregnant women than for other patients, and this factor may bias some of the reports of increased disease severity (Kourtis et al., 2014).

A recent Irish National Guideline has introduced a classification of infections in pregnancy. It classifies one group of infections specific to pregnancy: (Health Service Executive & Institute of Obstetricians & Gynaecologists, 2015).

Table 1 Classification of Infections and Pregnancy (Turner, 2014)

A. Infections specific to pregnancy
   1. Chorioamnionitis
   2. Endometritis
   3. Wound infection post caesarean section
   4. Perineal infection
   5. Lactational mastitis

B. Infections exacerbated during pregnancy
   1. Urinary tract infection, including pyelonephritis
   2. Pneumonia
   3. Rubella
   4. Listeria
   5. Influenza
   6. Varicella
   7. Toxoplasmosis
   8. Herpes infection
   9. Parvovirus
   10. Cytomegalovirus (CMV)

C. Infections incidental to pregnancy, for example
   1. Viral hepatitis
   2. Human Immunodeficiency Virus (HIV)
   3. Sexually Transmitted Diseases (STDs)
   4. Tuberculosis
   5. Endocarditis

6.2 Immune system in pregnancy

During pregnancy, immunological adaptations are required to accommodate the fetus (Kourtis et al., 2014). It is not only the maternal immune system that is responding to infection but also the fetal/placental unit. It has been suggested that the placenta and the fetus affect the global response of the mother to microbial infection (Cardenas et al., 2010). In pregnancy, the placenta functions not only as a simple mechanical barrier but also as an active functional barrier capable of recognising self from non-self and coordinating the maternal immune response (Mor, 2008). Although substantial progress has been made in the understanding of the immunology of pregnancy, many unanswered questions remain, especially those associated with the susceptibility of mother and unborn children to infectious agents (Jamieson et al., 2009, Romero et al., 2002).

Immunologic changes during pregnancy may help explain the altered severity of and susceptibility to infectious diseases during pregnancy. As pregnancy progresses, hormone levels change dramatically and are considerably higher than at any other time. The interplay between sex hormones and the immune system is complex and multifactorial and affects many organ systems (Robinson and Klein, 2012). During pregnancy, it is advantageous for inflammatory immune responses that might lead to fetal rejection to be reduced and anti-inflammatory responses that promote transfer of maternal antibodies to the fetus to be increased (Robinson and Klein, 2012).

6.3 Prescribing antimicrobials

One of the least developed areas of clinical pharmacology and drug research is the use of medication during pregnancy and lactation (Buhimschi and Weiner, 2009a). Often the safety of a drug for mothers and their offspring cannot be determined until it has been widely used. The quantity and quality of pregnancy safety data varies with antibiotic. Because of this, conflicts can arise between the theoretical fear of adverse fetal or neonatal consequences and the general bias among healthcare professionals that the successful treatment of medical conditions in the woman is in the best interest of her baby (Nahum et al., 2006).

Pregnancy risk factors together with an increased incidence of chronic diseases and the rise in mean maternal age predict an increase in medication use during pregnancy (Buhimschi and Weiner, 2009b). Due to the potential for maternal and fetal side effects, antimicrobials should only be used when the indication is clear and the risk: benefit ratio justifies their use (Niebyl, 2003).

6.4 General Antimicrobial Prescribing advice

1. Prescribing guidelines are an aid to clinical practice and should not replace robust clinical judgement and local sensitivity and pathogen data.

2. Prescribing guidelines should be used in conjunction with local microbiological surveillance data.

3. All health care professionals who prescribe medication for women of child-bearing age should consider possible pregnancy before prescribing.

4. Where the woman has intrapartum pyrexia, there should be a low index of suspicion for investigating the neonate for sepsis.

5. The woman's allergy status should be established before antimicrobial treatment is prescribed.

6. Ideally, appropriate microbiological samples should be taken before antimicrobial treatment commences (e.g. blood cultures, urine, high vaginal swab).

7. Treatment should be reviewed when culture results become available.

8. If the woman does not improve on a particular course of antimicrobials, consider if an empirical switch is needed or another diagnosis may be present.

9. The oral route is the preferred route of administration except in severe infection, or if the woman is unable to tolerate oral medications e.g. due to emesis.

10. Avoid unnecessarily prolonged courses of antimicrobials and switch to the oral route as soon as clinically appropriate.

11. Adjust dose appropriately after considering age, weight and hepatic or renal function.

12. Be aware of the risk of *Clostridium difficile* infection in women undergoing all antimicrobial treatment and seek specialist advice if necessary.

13. Be aware of the possibility of Q-T elongation caused by medication (e.g. quinolones), seek advice if necessary.

14. Use generic antimicrobial names as standard when prescribing.

15. Comprehensive individual drug information including drug interaction, adverse effects and contraindications is available from product insert literature, at www.medicines.ie , www.hpra.ie and reliable references sources e.g. Irish National Formulary and British National Formulary (BNF).

16. Adverse effects of antimicrobials should be notified to the Health Product Regulatory where appropriate using the designated notification card.

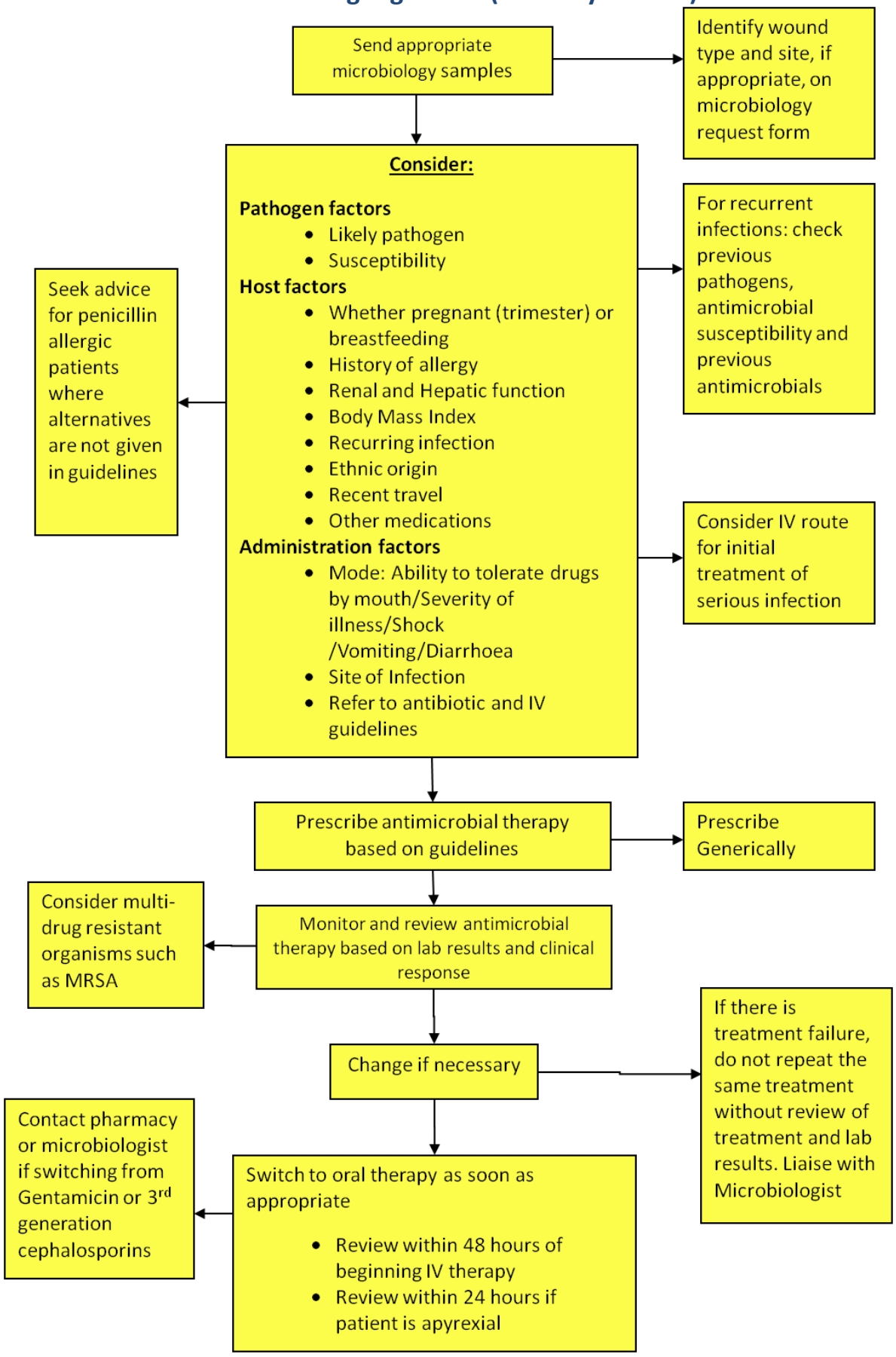
17. Consult local sensitivity data and seek expert advice if the mother is a known carrier of a multi-drug resistant organism e.g. VRE (vancomycin resistant Enterococcus), ESBLs (extended spectrum β-lactamase producing Gram negative bacilli), CRE (carbapenem resistant enterobacteriaceae) or MRSA (methicillin resistant *Staphylococcus aureus*). Also consider these organisms in women who have been transferred from another healthcare facility.

18. Consider unusual or atypical organisms in women who have returned from travel abroad.

19. Give special consideration to immune compromised women or women with morbidities that may compromise antimicrobial treatment and infection e.g. HIV, Transplant patient, patient on long term immune suppressants, CF patients, haematological disorders, patients with chronic renal or hepatic impairment etc.

20. When considering treatment with antibacterial agents during pregnancy, the following factors should be taken into account: the severity of the maternal infection, the presence of sepsis, the maternal and fetal risks associated with failing to treat the mother adequately, the pharmacokinetic and pharmacodynamic effects (where known) of pregnancy on drug absorption, distribution, metabolism and excretion, and the potential fetotoxicity of the treatments being considered.

6.5 Antimicrobial Prescribing Algorithm (courtesy CWIUH)



6.6 Useful websites when considering toxicity in pregnancy and lactation

- National Clinical Guidelines in Obstetrics and Gynaecology. Available from http://www.hse.ie/eng/about/Who/clinical/natclinprog/obsandgynaeprogramme/obsgyneguide.html
- Health Protection Surveillance Centre. Available at http://www.hpsc.ie/
- The Health Products Regulatory Authority. Available from : https://www.hpra.ie/
- UK Teratology Information Service (UKtis) abstracts: Available at http://www.uktis.org/html/maternal_exposure.html. Subscription required for full text.
- Reproductive Toxicology Center. REPROTOX Washington [cited 2015 July]. Available from: www.reprotox.org.
- Royal College of Obstetrics and Gynaecology. Available from: www.rcog.org.uk
- Medicines.ie. Medicines.ie Available from: www.medicines.ie.

7 Antimicrobial Stewardship

7.1 Introduction

Infections with antibiotic-resistant bacteria result in increased patient morbidity and mortality as well as increased hospital length of stay (Melzer and Petersen, 2007, Cosgrove and Carmeli, 2003, Roberts et al., 2009). Antibiotic resistance frequently leads to a delay in appropriate therapy (Kollef et al., 1999).

Inappropriate or delayed antibiotic therapy in patients with severe infections is associated with worse outcomes and sometimes death (Ibrahim et al., 2000, Lodise et al., 2003, Alvarez-Lerma, 1996). As antimicrobial resistant increases, clinicians are faced with additional treatment challenges (Jolley and Wing, 2010).

Antimicrobial stewardship refers to coordinated interventions and strategies designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration. Antimicrobial stewards seek to achieve optimal clinical outcomes related to antimicrobial use, minimize toxicity and other unintended adverse events, reduce the costs of health care for infections, and limit the selection for antimicrobial resistant strains (Jolley and Wing, 2010).

A working group of the Strategy for the control of Antimicrobial Resistance in Ireland (SARI) produced recommendations for development of antimicrobial stewardship programmes in hospitals in 2003. These recommendations have been updated, in light of more recent evidence and international guidelines and are available at the HPSC website (SARI Hospital Antimicrobial Stewardship Working Group, 2009). The IDSA (Infectious Disease Society of America) also produced guidelines for the development of institutional programmes to enhance antimicrobial stewardship (Dellit et al., 2007). Antimicrobial Stewardship programmes are now being assessed as KPIs by HIQA during their inspection of hospitals.

Antimicrobial Stewardship initiatives can include the following (Deuster et al., 2010, SARI Hospital Antimicrobial Stewardship Working Group, 2009)

- Formalised prescribing guidelines
- Formulary or antimicrobial prescribing restriction
- Education Programmes
- Drug utilisation audits and reviews e.g. PPS (Point Prevalence survey)
- Antibiotic consulting teams
- Computerised clinical decision support systems
- Regular identification and analysis of local pathogens and infection and resistance patterns
- Monitoring changes in patient demographic profiles
- Monitoring patient case mix
- Changes in infection control measures or their intensity
- Matching the most appropriate antimicrobial to a specific patient during pregnancy, renal impairment etc.

Antimicrobial Stewardship programmes are not simply a means to reduce drug consumption or to promote cost containment, but are also strategies to enhance patient safety by minimising exposure to drugs, performing dose adjustments, eliminating redundant therapy and targeting treatment to likely pathogens (Deuster et al., 2010).

Through the reduction in prescribing of restricted, often costly antimicrobials, cost efficiencies may occur. Antimicrobial stewardship programmes can achieve a sustained change in clinical practice and are appropriate for teaching and establishing good therapeutic practices and are more likely to be effective when local conditions are considered (Deuster et al., 2010).

7.2 Appropriate Intravenous to Oral Antibiotic switch

The ideal route of administration for any medication is one that achieves serum concentrations sufficient to produce the desired effect without producing undesired effects. In the past, patients were switched to oral (PO) therapy to continue treatment after an already adequate course of intravenous (IV) therapy was administered.

Today, it is not uncommon to convert a patient to PO therapy as part of the initial treatment course. The available oral formulations on the market are easier to administer, safe, and achieve desired therapeutic concentrations, thus making the PO route an ideal choice.

The IV and oral dosage ranges in the table below are **not** directly equivalent and should be used for guidance only in conjunction with clinical assessment of each individual case and expert advice where required. Prescribers should refer to the individual medication SPC available at www.medicines.ie and www.hpra.ie for specific pharmacokinetics, pharmacodynamics and bioavailability information.

7.3 Examples of IV to PO administration switches

IV Antibiotic	***Appropriate oral switch***
Amoxicillin 500mg-1g 6 – 8 hourly	Amoxicillin 500mg - 1g 6 – 8 hourly
Benzylpenicillin 1.2g 6 hourly	Amoxicillin 500mg - 1g 6 – 8 hourly
Cefotaxime 2g 12 hourly	Cefuroxime axetil 250-500mg 12 hourly
Cefuroxime 750mg – 1.5g 6-8 hourly	Cefuroxime axetil 250-500mg 12 hourly
Ciprofloxacin 400mg 12 hourly	Ciprofloxacin 250 –750mg 12 hourly
Clarithromycin 500mg 12 hourly	Clarithromycin 500mg 12 hourly
Co-amoxiclav 1.2g 8 hourly	Co-amoxiclav 375mg – 625mg 8 hourly
Clindamycin 600-900mg 8 hourly	Clindamycin 300-450mg 6 hourly
Erythromycin 500mg 6 hourly	Erythromycin 500mg 6 hourly
Flucloxacillin 1-2g 4 – 6 hourly	Flucloxacillin 500mg – 1g 6 hourly
Gentamicin	Follow isolate sensitivities/Contact Microbiologist or Pharmacy for advice
Metronidazole 500mg 8 hourly	Metronidazole 400mg 8 hourly
Vancomycin	Follow isolate sensitivities/Contact Microbiologist or Pharmacy for advice

8 Penicillin Allergy in Pregnancy

8.1 Introduction

Penicillin "allergy" history, although often inaccurate, is not a benign finding at hospital admission. Studies have shown that people with a label of penicillin allergy are more likely to be treated with broad-spectrum, non-penicillin antibiotics, such as quinolones, vancomycin and third-generation cephalosporins (Dworzynski et al., 2014). Use of these antibiotics in people with an unsubstantiated label of penicillin allergy may lead to antibiotic resistance and, in some cases, sub-optimal therapy (Dworzynski et al., 2014).

The Guidelines for Antimicrobial Prescribing in Primary Care in Ireland website has a useful section on verifying penicillin allergy which is available at http://www.antibioticprescribing.ie/useful-info/tips-on-verifying-penicillin-allergy.

8.2 What is a drug allergy?

All drugs have the potential to cause side effects, also known as 'adverse drug reactions', but not all of these are allergic in nature. Other reactions are idiosyncratic, pseudo-allergic or caused by drug intolerance. The mechanism at presentation may not be apparent from the clinical history and it cannot always be established whether a drug reaction is allergic or non-allergic without investigation.

Immunological responses to penicillin and other beta-lactam antibiotics can be broadly classified as ‘Immediate’ and ‘non-immediate’ or delayed based on the temporal association of onset of symptoms following drug administration. While ‘immediate’ responses are IgE mediated and generally occur within minutes to 1 h following exposure to the last dose, ‘non-immediate ’reactions are non-IgE-mediated and manifest generally more than 60 min to several days after last dose administration (Mirakian et al., 2015). The latter group is heterogeneous with respect to clinical manifestations and underlying immunological mechanisms and can range from superficial rashes to severe rashes such as Stevens-Johnson syndrome.

Some examples of definitions of allergy are as follows:

- " any reaction caused by a drug with clinical features compatible with an immunological mechanism"(Dworzynski et al., 2014).
- "drug allergy is an adverse drug reaction with an established immunological mechanism (Dworzynski et al., 2014).
- "An immunologically mediated response to a pharmaceutical and/or formulation (excipient) agent in a sensitized person (Joint Task Force on Practice Parameters; American Academy of Allergy, 2010).

8.3 Cross-reactivity

Antimicrobial type	**Reported allergy in penicillin allergic patients**
Cephalosporin 1st generation Plus cefaclor	2.5-10% reported (Lagace-Wiens and Rubinstein, 2012)
Cephalosporin 2nd generation Except cefaclor	Low (Mirakian et al., 2015)
Cephalosporin 3rd generation	Low (Mirakian et al., 2015)
Carbapenems	1% (Lagace-Wiens and Rubinstein, 2012)

8.4 Treatment options

There is a variety of recommendations and practice regarding the use of cephalosporins in women with a history of penicillin allergy.

A recent survey, carried out on behalf of the British Society for Allergy and Clinical Immunology (BSACI), on the investigation and management of β-lactam hypersensitivity revealed a large heterogeneity among clinical practices and highlighted the urgent need for evidence-based national guidelines (Richter et al., 2013). This lead to the development of the BSACI "Management of allergy to penicillins and other beta-lactams" national guidelines (Mirakian et al., 2015). However, these guidelines do not cover penicillin allergy in the pregnant woman.

The ACOG recommend cefazolin, a first generation cephalosporin for the treatment of GBS in labour in women who have a penicillin allergy that does not include anaphylaxis, angioedema, respiratory distress and urticaria (Verani et al., 2010).

The American Academy of Pediatrics practice guidelines for the management of acute bacterial sinusitis and acute otitis media have recommended the use of second or third generation cephalosporins in women with a history of penicillin allergy who did not experience urticaria or anaphylaxis to penicillin (American Academy of Paediatrics Subcommittee on Management of Sinusitis and Committee on Improvement, 2001).

The American Joint Task Force on Practice Parameters have recommended penicillin skin testing to determine the risk of a cephalosporin reaction in women with a history of penicillin allergy (Joint Task Force on Practice Parameters; American Academy of Allergy, 2010).

The RCOG recommend treating a pregnant women reporting any penicillin allergy with clindamycin for the prevention of Group B early-onset disease Streptococcal Disease in neonates (Royal College of Obstetrics and Gynaecology, 2012)

A Spanish study in 2001 suggested that penicillin allergic women may receive cephalosporins with a low risk of an allergic reaction, provided that cephalosporins with a different side chain to that of the penicillin responsible for the allergic reaction are used and administered under careful supervision (Novalbos et al., 2001).

8.5 In conclusion

There is no general consensus on treatment options for pregnant women or indeed the general population with a reported mild penicillin allergy as illustrated by the Table below:

Expert body	What to give pregnant women with a penicillin allergy either mild or any allergy , as alternative to penicillin
RCOG	Use Clindamycin (Royal College of Obstetrics and Gynaecology, 2012)*
ACOG	Cephalosporin (American College of Obstetricians and Gynecologists, 2011)
CDC	Cefazolin(cephalosporin) (Cagno et al., 2012)

Current recommendations regarding cephalosporin use in penicillin allergic pregnant women may be summary

Therefore, it may be prudent not to give cephalosporins to pregnant women who report any penicillin allergy, particularly if the woman is acutely ill.

Research is required to inform a national standard for Ireland on how to prescribe antimicrobials to patients with penicillin allergy who are pregnant.

9 Antimicrobial Resistance

9.1 Introduction

Due to the continually expanding problem of antibacterial resistance worldwide, prescribers are often faced with challenging situations when they treat patients with infections.

This is of greater significance in the area of obstetrics, where the prescriber is prescribing an antibiotic for the expectant mother with the accompanying exposure of the developing fetus to this antibiotic. Healthcare providers have been forced to prescribe a wider array of newer antibiotics for pregnant women with limited information on safety during pregnancy (Crider et al., 2009). It is essential, therefore, in order to help limit the rise of antibiotic resistance that clinicians prescribe the most narrow spectrum antibiotic clinically possible using the most efficacious regimen.

The following Tables summarise available information for the most commonly experienced resistance issues in obstetric settings in Ireland.

9.2	Methicillin resistant Staphylococcus aureus
Organism	*Staphylococcus aureus* is a Gram-positive coccus that is most commonly found in the nose, throat and on the skin. It can cause skin infections such as cellulitis, wound infections as well as more complicated infections such as osteomyelitis and endocarditis.
Acronym	MRSA
Prevalence	For Q1-2 2014, The proportion of *S.aureus* bacteraemia cases that were MRSA had increased to 21% (EARS-Net report Quarters 1-2, 2014).However, in a retrospective study of MRSA in a British maternity hospital the incidence of MRSA carriage was only 0.5%(Gray and Suviste, 2013)
Risk factors	Some risk factors for MRSA carriage are: • Previous antimicrobial use(Gonzalez-Castillo et al., 2013, Gross et al., 2014) • Long-term admission to hospital(Gross et al., 2014) • Healthcare workers(Verwer et al., 2012) • Indwelling devices (e.g. catheter) (Gonzalez-Castillo et al., 2013)
Impact on antimicrobial choice	β-lactam antimicrobials, such as co-amoxiclav, cefuroxime and flucloxacillin, are not effective against MRSA. This is because of the presence of a *mecA* gene which encodes for the altered penicillin binding protein PBP2a. The *mecA* gene is carried on a mobile genetic element called the Staphylococcal chromosomal cassette (*SCCmec*). Hospital acquired strains are typically only susceptible to vancomycin and linezolid. Community acquired strains may also be susceptible to clindamycin, trimethoprim and clarithromycin. Treatment should be guided by antimicrobial susceptibility results.
Infection control precautions	Contact precautions and isolation in a single room
Suggested Guidelines	Prevention and Control Methicillin resistant Staphylococcus aureus (MRSA). National clinical guideline No. 2 (2013) (National Clinical Effectiveness Committee, 2013)
Patient leaflet available	Yes http://www.hpsc.ie/A-Z/MicrobiologyAntimicrobialResistance/EuropeanAntimicrobialResistanceSurveillanceSystemEARSS/ReferenceandEducationalResourceMaterial/SaureusMRSA/Factsheets/ (last accessed 18/2/2015)
Notes	Some MRSA isolates possess the Panton-Valentine-Leukocidin (PVL) toxin, particularly some community acquired strains which are circulating in North America. These strains can cause recurrent boils or in certain cases lead to necrotising pneumonia. Clinical laboratories do not routinely test for the presence of PVL toxin, but it should be considered in patients presenting with severe necrotising pneumonia or with a history of recurrent boils in the household.

9.3	Vancomycin resistant Enterococci
Organism	Enterococci are Gram-positive cocci that are commonly found in the gastrointestinal tract of patients, particularly in the large bowel. They can cause urinary tract infections in pregnant patients and can play a role in complex intra-abdominal infections. There are two main species of Enterococcus; *Enterococcus faecalis* which is usually amoxicillin susceptible and *Enterococcus faecium* which is usually amoxicillin resistant.
Acronym	VRE
Prevalence	For Q1-2 2014, The proportion of *E.faecium* bacteraemia cases that were vancomycin resistant had increased to 45.9% (EARS-Net report Quarters 1-2, 2014). It should be noted that Ireland is the only country in Europe where the proportion of *E.faecium* bacteraemia cases resistant to vancomycin is over 25%.
Risk factors	Risk factors for VRE carriage include duration of previous hospitalisation and previous glycopeptides usage (Papadimitriou-Olivgeris et al., 2014)
Impact on antimicrobial choice	Several clusters of genes (e.g. *VanA*, *VanB*, *VanD*) can encode for vancomycin resistance in Enterococci. They result in a change in the terminal sub-unit binding protein resulting in a significantly reduced binding affinity for vancomycin. There are a limited range of antimicrobials available to treat VRE infections. Daptomycin and linezolid are two treatment options, however, there is very little data on the safety of these drugs in pregnancy or the lactating mother.
Infection control precautions	Contact precautions and isolation in a single room
Suggested Guidelines	Guidelines for the Prevention and control of multi-drug resistant organisms (MDRO) excluding MRSA in the healthcare setting. (Royal College of Physicians clinical advisory group on Healthcare Associated Infections in association with HSE Quality and Patient Safety, 2012)
Patient leaflet available	Yes http://www.hpsc.ie/A-Z/MicrobiologyAntimicrobialResistance/EuropeanAntimicrobialResistanceSurveillanceSystemEARSS/ReferenceandEducationalResourceMaterial/EnterococciVRE/Factsheet/ (last accessed 18/2/2015)
Notes	The incidence of VRE is very low in the maternity setting due to the fact that most patients have previously been well and are unlikely to have had vancomycin exposure. Screening for VRE is not routinely carried out in maternity patients, however screening of neonates may be considered.

9.4	Clindamycin resistant Group B Streptococci
Organism	Group B Streptococcus (GBS) is one of the most significant pathogens in the maternity setting. It is a Gram-positive coccus which can cause both maternal and neonatal sepsis. Of note with neonates, is that it can cause early-onset infections leading to sepsis, meningitis and possibly death
Acronym	No standard acronym
Prevalence	Surveillance studies in the United States of America have shown that the rate of clindamycin resistance in Group B Streptococcus from obstetric patients is between 33% and 38% (DiPersio and DiPersio, 2006, Back et al., 2012).
Risk factors	A Korean study has shown that previous sore throat and premature rupture of the membranes are associated with a higher risk of clindamycin resistant Group B Streptococcus (Yook et al., 2013). This may be due to the fact that these patients may have been exposed to macrolides as treatment, particularly if penicillin allergic.
Impact on antimicrobial choice	Clindamycin resistant Group B Streptococcus is a major issue for maternity services. For penicillin allergic patients requiring intrapartum antimicrobial prophylaxis, clindamycin is the first choice, however if there is a history of clindamycin resistant GBS then vancomycin should be used.
Infection control precautions	Standard precautions
Suggested Guidelines	• The prevention of early-onset neonatal group B Streptococcal disease (Green-top guideline No. 36) (Royal College of Obstetrics and Gynaecology, 2012) • Centers for Disease Control and Prevention. Prevention of perinatal group B Streptococcal disease. MMWR 2010; 59: RR-10(Verani et al., 2010)
Patient leaflet available	Yes https://www.rcog.org.uk/globalassets/documents/patients/patient-information-leaflets/pregnancy/pi-groupb-streptococcus-gbs-infection-in-newborn-babies.pdf (last accessed 18/2/2015)
Notes	Maternity hospital should determine their own local clindamycin resistant Group B Streptococcal rates and use this information to inform their policy for performing antimicrobial susceptibility testing and also on what intrapartum antimicrobial regimen to use in patients with penicillin allergy.

9.5 Extended spectrum β-lactamases

Organism	Extended spectrum β-lactamases are enzymes found in Gram-negative organisms such as *E.coli* and *Klebsiella pneumoniae* that can confer resistance to β-lactams such as cephalosporins.
Acronym	ESBL
Prevalence	In Q1-2 2014, the proportion of *E.coli* bactaeraemia due to ESBL producing *E.coli* was 10.6% while 18.4% of *Klebsiella pneumoniae* bacteraemia were due to ESBL producing strains (EARS-Net report Quarters 1-2, 2014).
Risk factors	Risk factors for ESBL carriage according to the national multi-drug resistant organism guidelines are: • Previous hospital admission • Exposure to broad spectrum antimicrobials • ICU admission • Presence of vascular catheters or urinary catheters
Impact on antimicrobial choice	Cephalosporins should not be used to treat infections due to ESBL producing organisms. Although β-lactamase inhibitor drugs (e.g. amoxicillin-clavulanate and piperacillin-tazobactam) can be used to treat certain infections due to ESBL producing organisms this should be done with extreme caution in pregnancy. Carbapenems (e.g. meropenem) are the antimicrobials of choice for ESBL producing organisms, however quinolones and aminoglycosides may also be used if susceptible in certain situations.
Infection control precautions	Contact precautions and a single isolation room
Suggested Guidelines	Guidelines for the Prevention and control of multi-drug resistant organisms (MDRO) excluding MRSA in the healthcare setting; (Royal College of Physicians clinical advisory group on Healthcare Associated Infections in association with HSE Quality and Patient Safety, 2012)
Patient leaflet available	Yes http://www.hpsc.ie/A-Z/Other/ESBL/Factsheet/ (last accessed 18/2/2015)
Notes	If a baby, from a mother who carries ESBL producing organisms, is admitted to the NICU then the neonatology team should be informed of the mother's carriage status. This is particularly important as the current empirical treatment regimens used in most NICUs may not be effective against ESBL producing organisms. Babies who are admitted to the NICU in this situation should be discussed on a case-by-case basis.

9.6	Carbapenemase producing Enterobacteriaceae
Organism	Carbapenemase producing Enterobacteriaceae are Gram-negative organisms such as *E.coli* and *Klebsiella pneumoniae*, that possess a carbapenemase enzyme which can hydrolyse β-lactams including carbapenems such as meropenem.
Acronym	There is no standard acronym as CPE and also CRE have been used. There are also several types of carbapenemases which have their own acronyms (e.g. KPC, VIM, IMP, and OXA).
Prevalence	In Q1-2 2014, the proportion of *Klebsiella pneumoniae* bacteraemia which were carbapenem resistant was 1.8% (EARS-Net report Quarters 1-2, 2014). The incidence of these organisms is very low in the maternity settings (<1%).
Risk factors	Risk factors for CRE carriage are similar to those for ESBL carriage, however admission to hospitals abroad such as in the Indian Sub-continent and North America should also be considered.
Impact on antimicrobial choice	There is limited data on the optimal treatment regimen for infections due to carbapenemase producing Enterobacteriaceae. The treatment of individual patients must be done in consultation with Microbiologists and Infectious Disease Physicians.
Infection control precautions	Individual hospitals will have local policies for this situation and the Infection Control Team of the hospital should be contacted for advice.
Suggested Guidelines	Guidelines for the Prevention and control of multi-drug resistant organisms (MDRO) excluding MRSA in the healthcare setting (Royal College of Physicians clinical advisory group on Healthcare Associated Infections in association with HSE Quality and Patient Safety, 2012)
Patient leaflet available	Yes http://www.hpsc.ie/A-Z/MicrobiologyAntimicrobialResistance/StrategyforthecontrolofAntimicrobialResistanceinIrelandSARI/CarbapenemResistantEnterobacteriaceaeCRE/Factsheets/ (last accessed 18/2/2015)
Notes	Although very rare in the maternity setting, hospitals should be vigilant for patients carrying these organisms as they have the ability to cause significant outbreaks. Local policies should exist for dealing with the infection control precautions and antimicrobial management should be tailored to the individual patient.

10 Viral Infections and Syphilis

This set of guidelines does not intend to cover the investigation and management of viral infections in pregnancy, as this is covered comprehensively in other national and international guidelines which are highlighted below.

Virus	Irish guidelines	Weblinks
CMV	Cytomegalovirus infection in Pregnancy, Society of Obstetricians and Gynaecologists of Canada Practice Guideline. JOGC 2010; 240: 348-354	http://sogc.org/wp-content/uploads/2013/01/gui240CPG1004E.pdf
Parvovirus	Parvovirus B19 infection exposure during pregnancy. Institute of Obstetricians and Gynaecologists, Royal College of Physicians of Ireland and the Health Service Executive 2014	http://www.hse.ie/eng/about/Who/clinical/natclinprog/obsandgynaeprogramme/parvovirus.pdf
Chickenpox	Varicella in Pregnancy guideline. Institute of Obstetricians and Gynaecologists, Royal College of Physicians of Ireland and the Health Service Executive 2015	http://www.hse.ie/eng/about/Who/clinical/natclinprog/obsandgynaeprogramme/obsgyneguide.html
HIV, Hepatitis B/C, Syphilis and HSV	Mother to Child Transmission guidelines. Rainbow clinic 2015	http://www.ssstdi.ie/guidelines/

11 Parasitic Infections – Malaria

Due to the challenges discussed above and the fact that a woman is unlikely to be newly diagnosed with malaria in the Irish obstetric setting, we feel that the management of malaria is beyond the scope of this document. The treatment of malaria in a pregnant woman is a complex issue and requires multidisciplinary input, particularly from infectious disease specialists.

Below however, a list of recommended reading and guidelines has been included which should aid clinicians in managing these infections. Local infection specialists should be involved in cases at an early stage along with senior obstetricians and where required, national infectious disease experts.

Organism	**Suggested guidelines to consider**	
Malaria	The diagnosis and treatment of malaria in pregnancy. Royal College of Obstetricians and Gynaecologists Green-top guideline No. 54bn (2010)	https://www.rcog.org.uk/globalassets/documents/guidelines/gtg54bdiagnosistreatmentmalariapregnancy0810.pdf
	Guidelines for the treatment of malaria. World Health Organization (Third edition) 2015	http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127_eng.pdf?ua=1&ua=1

12 Therapeutic Drug Monitoring

12.1 Gentamicin

12.1.1 Introduction

Aminoglycosides have relatively poor distribution into many tissues, including the lungs. They have minimal nervous system penetration. This makes them less than optimal as monotherapy for many severe infections. The “booking “actual body weight is often used for dose calculation. Consideration should be given to using an adjusted body weight in morbid obesity, serious overdosing of patients can occur if the patients total body weight is used (Gallagher and Mac Dougall, 2014). Calculation could be based on IBW (South Australian Maternal and Neonatal Clinical Network, 2014) as gentamicin distributes poorly into adipose tissue.

➔ Female Ideal Body Weight = 45.5 kg + 0.9 kg (for each cm over 152 cm)

Aminoglycosides have a narrow therapeutic window, therefore safe and effective therapy requires accurate dose selection and time sensitive serum level monitoring. Failure to achieve optimal dosing runs the risk of increased patient morbidity, mortality and increase resistance. Incorrect dosing carries the risk of significant toxicity, primarily nephrotoxicity and ototoxicity, through its potential to cause kidney or eighth cranial nerve damage in the mother or neonate (Locksmith et al., 2005). Gentamicin half-life is decreased in pregnant women due to the increased volume of distribution and increased GFR. A maximum daily dose of 480mg is sometimes suggested in women with normal renal function.

Research is needed urgently to confirm the efficacy and toxicity profile of different treatment frequencies on the mother and fetus and help elucidate the pharmacokinetics of gentamicin in pregnancy.

12.1.2 Gentamicin level monitoring

Monitoring aminoglycoside serum levels can help guide appropriate dosing by avoiding both excessive and subtherapeutic concentrations thus reducing the risk of toxicity, and ensuring efficacy. However, for accurate serum concentrations, samples must be drawn correctly

and at the right time to thus allow useful interpretation. High serum level results can result from blood samples being taken too early or as a result of the blood sample being taken from the line that the gentamicin was administered through. Serum-aminoglycoside concentrations should be measured in all patients receiving parenteral aminoglycosides and must be determined in the elderly, in obesity, in patients with cystic fibrosis, where high doses are being given and in renal impairment (British Medical Association and Pharmaceutical Press, 2014-2015).

The main side effects of gentamicin are dose related, therefore care must be taking with dosage and wherever possible treatment duration should not exceed 7 days (British Medical Association and Pharmaceutical Press, 2014-2015).

12.1.3 Optimum gentamicin dosing in pregnancy

Fear of toxicity can result in sub-therapeutic gentamicin dosing and error in therapeutic drug monitoring performance can also lead to unintended dose omission or delay. These factors can contribute to risk of treatment failure and emergence of gentamicin resistance (HSE National Quality Improvement Programme, 2014).

12.1.4 Once daily dosing

Once-daily or extended-interval aminoglycoside dosing uses the concentration dependent killing of the drug to create an equally effective, more convenient and possibly safer regimen.

However, there are many populations in which once-daily dosing has had limited research, including pregnant women, the critically ill, those with significant renal dysfunction and the morbidly obese. Therefore this dosing method should be used in caution in these populations (Gallagher and Mac Dougall, 2014, British Medical Association and Pharmaceutical Press, 2014-2015). Patients with myasthenia gravis should not receive gentamicin.

Administering the total daily dose of gentamicin once daily instead of divided doses e.g. every 8 hours has been suggested as a method of reducing toxicity (Gallagher and Mac

Dougall, 2014). It has been suggested that once daily administration is less nephrotoxic though the effect on ototoxicity remains less clear (Ariano et al., 2008, Drusano et al., 2007).

Locksmith et al study of extended-interval versus standard dosing of gentamicin in pregnant women at greater than 34 weeks of gestation demonstrated peak maternal gentamicin serum concentrations ranging from 13 to 25µ/ml after a dose of 5.1mg/Kg (Locksmith et al., 2005). This study showed no adverse fetal effects as a result of the drug in either group. Locksmith et al suggest that since maternal drug concentrations are a major determinant of fetal concentrations, standard multiple daily dosing is preferred over extended-interval dosing because the latter regimen can result in supratherapeutic peak maternal serum glycoside levels (Locksmith et al., 2005).

Once daily gentamicin dosing is the gold standard for the non-pregnant patient with normal renal function, however the evidence for once daily use in pregnancy is lacking, the BNF states “There is insufficient evidence to recommend a once daily, high-dose regimen of an aminoglycoside in pregnancy” (British Medical Association and Pharmaceutical Press, 2014-2015). Despite this many maternity centres have moved to once daily dosage for gentamicin, as administration is more convenient, accurate TDM is facilitated and the incidence of late or missed doses is reduced.

12.1.5 Serum gentamicin monitoring in once daily administration

For once daily gentamicin administration, trough or pre-dose level is required 18-24 hours after the first dose. Suggested target peak levels are 16-24 mg/L and target trough levels are less than 1 mg/L (Gilbert, 2014). Many centres do not routinely measure peak levels for once daily dosage regimen. If levels are outside these ranges or renal impairment is present contact microbiology or pharmacy. For further recommendations on monitoring and dosing see the individual product’s manufacturer information on www.medicines.ie or www.hpra.ie.

12.1.6 Three times daily gentamicin dosing

Nahum et al in their 2006 review article found evidence for lower measured circulating drug concentrations for 4 antibiotics including gentamicin in pregnant women compared to nonpregnant women (Nahum et al., 2006). They suggested that a shorter dosing interval or increased maternal dose or both may be necessary to obtain similar circulating drug concentrations as for women in the nonpregnant state (Nahum et al., 2006).

Briggs recommends that standard aminoglycoside dosing should be avoided in pregnant women, as the extended-interval regimen is preferred in those patients with predictable volumes of distribution and drug clearance (Briggs and Wan, 2006). As a result of the physiological changes that occur in pregnancy and the more complicated pharmacokinetic profiles of medications, closer monitoring of serum gentamicin levels with more frequent administration schedules maybe warranted in pregnant women to avoid toxicity and lack of efficacy.

It has been suggested that since maternal drug concentrations are a major determinant of fetal concentrations, standard multiple daily dosing is preferred over extended-interval dosing because the latter regimen can result in supratherapeutic peak maternal serum glycoside levels (Locksmith et al., 2005).

12.1.7 Serum gentamicin monitoring for three times daily administration

The BNF suggests peak sampling 1 hour after intravenous administration and trough sampling just before the next dose (British Medical Association and Pharmaceutical Press, 2014-2015). Briggs suggests that peak maternal serum concentrations should not exceed normal therapeutic levels because of concerns of fetal toxicity (Briggs and Wan, 2006). Suggested target peak levels are 4-10 mg/L and target trough levels are 1-2 mg/L (Gilbert, 2014). If levels are outside these ranges or renal impairment is present contact microbiology or pharmacy.

If the trough concentration is high, the interval between doses should be increased. If the peak concentration is high, the dose should be decreased (British Medical Association and

Pharmaceutical Press, 2014-2015). Once renal function is normal, urine output is normal, there are no signs of toxicity and the clinician is happy with the patient's progress, gentamicin levels can then be checked twice weekly.

Renal functions should be checked at least three times a week. If renal function deteriorates then renal function should be checked daily and gentamicin levels closely monitored. Dose reduction may be required. For further recommendations on monitoring and dosing see the individual product's manufacturer information on www.medicines.ie or www.hpra.ie.

12.1.8 Table summary gentamicin:

Dose	Weight used	Peak level	Trough level
5mg/Kg / once a day Max dose 480mg/day	Booking weight (Reduce dose if obese)	Not routinely used for OD dosing. Unless concerned about efficacy or toxicity.	18-24 hours after 1st dose. Target levels : <1mg/L
5mg/Kg day in three divided doses Max dose 480mg/day	Booking weight (Reduce dose if obese)	One hour after IV administration Target levels : 4-10 mg/L	Before 3rd or 4th dose Target levels : <1mg/L

12.1.9 Ototoxicity

Aminoglycosides cause dose related cochlear and vestibular toxicity. For women anticipated to receive long-term treatment (>2 weeks), baseline and follow-up audiology are necessary. This ototoxicity is not reversible and can significantly affect quality of life, therefore it is important to monitor women closely for any hearing loss or balance problems(Gallagher and Mac Dougall, 2014). The reported range of hearing loss ranges from 0-27% (HSE National Quality Improvement Programme, 2014).

Carriers of the mitochondrial DNA mutation m.1555A→G may develop permanent, profound hearing loss after receiving aminoglycosides, even when drug levels are within the therapeutic range, with incidence of the mutation estimated at 1 in 500 (Bitner-Glindzicz et al., 2009).

12.1.10 Nephrotoxicity

Renal function is measured either in terms of estimated glomerular filtration rate (eGFR) calculated from a formula derived from the Modification of Diet in Renal Disease Study (MDRD) or it can be expressed as creatinine clearance. The latter ideally is derived from a 24 hour urine collection but often calculated from the Cockcroft and Gault formula (CG).

The serum-creatinine concentration is sometimes used as a measure of renal function but it is only a rough guide to drug dosing (BNF 69 - British Medical Association and Pharmaceutical Press, 2015). The BNF recommends using eGFR for most drugs and most patients over 18 of average build and height to determine dose adjustments. For toxic drugs with a narrow therapeutic index, the BNF recommends creatinine clearance calculated from CG formula should be used be used to determine dose adjustments (BNF 69 - British Medical Association and Pharmaceutical Press, 2015). For patients at extremes of body weight, for example BMI < 18.5kg/m^2 or BMI > 30kg/m^2 the BNF recommends the absolute GFR or creatinine clearance calculated from CG formula should be used. The UK Renal Association Kidney Disease Outcomes Quality Initiative (KDOQI) stages of chronic kidney diseases are illustrated in Table 1.

Oliguric acute renal failure, preceded by a rising serum creatinine, is a dose-related adverse effect of aminoglycosides. Risk may be reduced by correct dosing, including the use of extended-interval dosing, as well as the avoidance of co-administration of other nephrotoxins. e.g. vancomycin (Gallagher and Mac Dougall, 2014). The reported risk of nephrotoxicity ranges from 10-25% (HSE National Quality Improvement Programme, 2014).

Table 1: UK Kidney Association – KDOQI stages of CKD (2013)

stage	GFR*	Description	Treatment stage
1	**90+**	Normal kidney function but urine findings or structural abnormalities or genetic trait point to kidney disease	Observation, control of blood pressure. More on management of Stages 1 and 2 CKD.
2	**60-89**	Mildly reduced kidney function, and other findings (as for stage 1) point to kidney disease	Observation, control of blood pressure and risk factors. More on management of Stages 1 and 2 CKD.
3A **3B**	**45-59** **30-44**	Moderately reduced kidney function	Observation, control of blood pressure and risk factors. More on management of Stage 3 CKD.
4	**15-29**	Severely reduced kidney function	Planning for end stage renal failure. More on management of Stages 4 and 5 CKD.
5	**<15 or on dialysis**	Very severe, or **end stage** kidney failure (sometimes call **established renal failure**)	Treatment choices. More on management of Stages 4 and 5 CKD.

* All GFR values are normalized to an average surface area (size) of 1.73m$^{2.}$ CKD Chronic kidney disease

12.2 Vancomycin

12.2.1 Introduction

Vancomycin is a glycopeptides antibiotic with bactericidal activity against aerobic and anaerobic Gram-positive bacteria. Vancomycin is a concentration-dependent (time-dependent) killer of Gram-positive pathogens but has lower penetrations into the ELF and respiratory secretions (Rybak et al., 2009a). Vancomycin has a long duration of action which means it can be given every 12 hours. Early use of vancomycin was associated with infusion-related toxicities, nephrotoxicity and possible ototoxicity (Rybak et al., 2009a). The most common vancomycin adverse effects are unrelated to serum drug levels and include fever, chills and phlebitis. Red man syndrome, which is associated with histamine release and manifest as tingling and flushing of the face, neck and upper torso is most likely to occur when larger doses are infused too rapidly e.g. >500mg over ≤ 30 minutes (Rybak et al., 2009a).

The practice of routine monitoring and adjustment of serum vancomycin drug concentrations has been the subject of intense debate for many years. The controversy has resulted from conflicting evidence regarding the use of serum vancomycin concentrations to predict and prevent drug induced toxicity and as a measure of effectiveness in treatment of infections (Liu et al., 2011) and the lack of well-designed randomised clinical evaluations (Rybak et al., 2009b).

This controversy has led to a variation in clinical practice ranging from infrequent or avoidance of monitoring to overzealous monitoring and dose amendment (Rybak et al., 2009b). Data from recent studies appear to suggest that vancomycin has little potential for nephrotoxicity or ototoxicity when used at conventional dosages for example 1g every 12 hours, unless it is given concomitantly with known nephrotoxic drugs or at very high doses (Rybak et al., 1990, Rybak et al., 1999, Lodise et al., 2008).

Joint adult Vancomycin guidelines were produced in 2009 by Infectious Diseases Society of America, the American Society of Health System Pharmacists and the Society of Infectious Diseases Pharmacists (Rybak et al., 2009b). However, there are continuing issues with vancomycin which include- perceived concerns of increased MICs, treatment failures and toxicity and lack of prospective randomized double-blinded trials upon which to base guidelines (Lomaestro, 2011).

12.2.2 Vancomycin level monitoring

TDM is usually carried out for vancomycin if duration of therapy is expected to exceed 3-5 days, or if there is renal impairment or concern regarding toxicity or therapeutic failure. Trough serum vancomycin concentrations are the most accurate and practical method of monitoring the effectiveness of vancomycin (Rybak et al., 2009b). A trough sample is collected immediately before the 4^{th} dose, assuming the dose is given at its regular dosing interval (sometimes collected before 3^{rd} dose also) and the patient has normal renal function.

A peak sample, though rarely indicated, is collected 1 hour after the end of the infusion. Available evidence does not support monitoring peak serum vancomycin concentrations to decrease the frequency of nephrotoxicity (Rybak et al., 2009a). Higher vancomycin trough levels are associated with increased risk of nephrotoxicity. Subsequent samples are analysed as clinically appropriate and more frequent sampling may be required for less haemodynamically stable patients (Liu et al., 2011).

Target vancomycin trough levels are 10-20mg/L for uncomplicated infections including skin, soft tissue, bone and joint non-MRSA infections in clinically stable patients. Target trough levels are 15-20mg/L are severe infections including MRSA pneumonia, bacteraemia, osteomyelitis; CNS infections or endocarditis and empiric therapy in patients with severe sepsis and septic shock (Rybak et al., 2009a). Though there are limited data to support the safety of sustained trough serum vancomycin concentrations of 15-20mg/L (Rybak et al., 2009a).

12.2.3 Summary Table: Vancomycin

Dose	Weight used	Peak level	Trough level
15mg/Kg BD (Max 2g/dose)	Booking weight	Not routinely used for OD dosing. Unless concerned about efficacy or toxicity.	Before the 3rd or 4th dose Target levels : 10-20mg/L in general or 15-20 mg/L in MRSA, Septicaemia or other complicated infections e.g. osteomyelitis, endocarditis
Consider loading dose 25mg/Kg in severe sepsis			

Local guidelines for therapeutic monitoring should also be reviewed.

13 Vaccines in Pregnancy

13.1 Introduction

Immunity is the ability of the human body to protect itself from infectious disease. The defense mechanisms of the body are complex and include innate (non-specific, non-adaptive) mechanisms and acquired (specific, adaptive) systems. Immunisation is administration of a vaccine to stimulate production of an immune response.

An inactivated vaccine is a vaccine that contains killed bacteria or viruses, or a portion thereof for example inactivated Polio vaccine (Royal College of Physicians of Ireland (RCPI), 2015). Live attenuated vaccine is a vaccine that contains a weakened strain of live bacteria or viruses that replicate in the body for example BCG and MMR vaccines (Royal College of Physicians of Ireland (RCPI), 2015). Recombinant vaccine is a vaccine produced through recombinant DNA techniques for example hepatitis B and human papillomavirus vaccine (Royal College of Physicians of Ireland (RCPI), 2015). A conjugate vaccine is one where a protein or polysaccharide antigen is linked to a carrier protein e.g. meningococcal C conjugate C vaccine (Royal College of Physicians of Ireland (RCPI), 2015). Sub unit vaccines contain only specific antigenic proteins of an infectious agent for example acellular pertussis and some influenza vaccines (Royal College of Physicians of Ireland (RCPI), 2015). The term non live vaccine can be used to describe conjugate, inactivated, recombinant and subunit vaccines (Royal College of Physicians of Ireland (RCPI), 2015).

The need for vaccination, particularly for hepatitis B, measles, mumps, rubella, varicella, diphtheria, tetanus and pertussis, should be assessed as part of any pre-conception health check. Where previous vaccination history or infection is uncertain, relevant serological testing can be undertaken to ascertain immunity to hepatitis B. Without documented evidence of measles vaccination women should be offered two doses of MMR vaccine one month apart outside of pregnancy (Royal College of Physicians of Ireland (RCPI), 2015).

Recommendations regarding vaccine use in pregnancy are made where the benefits of protection from vaccination outweigh the risks. The objective of vaccination during pregnancy is to protect the mother and, potentially, the fetus and newborn. Pregnant

women respond adequately to vaccines even though pregnancy is an immunologically altered state (Canada, 2014).

Maternal vaccination protects the mother from vaccine-preventable diseases that she otherwise may transmit to her fetus or infant. In addition, protective concentrations of maternal antibodies may be transferred to the fetus transplacentally, with the majority of transfer occurring during the third trimester. Maternal antibodies typically have a half-life of 3 to 4 weeks in the newborn, and progressively decrease during the first 6 to 12 months of life. Recommended infant immunisation schedules take into consideration the potential effect that maternally transferred antibodies may have on infant vaccinations (Canada, 2014).

There is a theoretical concern that vaccinating pregnant women with live vaccines may infect the fetus. Live attenuated viral vaccines are contraindicated in pregnant women because of the hypothetical risk of harm should vaccine virus replication occur in the fetus. There is no evidence that any live vaccine, including MMR, causes birth defects. However, since the theoretical possibility of fetal infection exists, live vaccines should be delayed until after delivery (Public Health England).

Since inactivated vaccines cannot replicate and therefore cannot cause infection in either the mother or the fetus, they are generally considered safe in pregnancy (Canada, 2014, Public Health England). Reactions following vaccination with inactivated vaccines are usually limited to the injection site. No increase in anaphylactic reactions or events that might induce preterm labour has been observed (Canada, 2014). There is no evidence of risk from vaccinating pregnant women or those who are breastfeeding with inactivated viral or bacterial vaccines or toxoids. There are no published data indicating that currently authorised inactivated vaccines are teratogenic or embryotoxic, or have resulted in specific adverse pregnancy outcomes (Plotkin SA, 2012).

Detailed information about specific vaccinations is available at www.medicines.ie and www.hpra.ie.

13.2 General Principles of Vaccination Use during Pregnancy

- Follow Immunisation Guidelines for Ireland available on http://www.hse.ie/eng/health/immunisation/hcpinfo/guidelines/
- The following vaccines are recommended in pregnancy
  - ➔ Seasonal influenza vaccine for pregnant women at any stage of pregnancy. Pregnancy increases the risk of complications from influenza because of the alterations in heart rate, lung capacity, and immunological function. Influenza in pregnancy is associated with premature birth and reduced fetal growth. Vaccination during pregnancy provides passive immunity to infants up to the first 6 months of life (Royal College of Physicians of Ireland (RCPI), 2015).
  - ➔ Pertussis vaccine for all pregnant women between 27-36 weeks gestation to reduce the risk of infection in the mother and to reduce the morbidity and mortality in infants too young to be vaccinated. Circulating maternal antibodies in the newborn protect them in the early weeks after birth. Pertussis vaccine is recommended on every pregnancy as maternal antibodies to pertussis wane and so will not provide protection in subsequent pregnancies (Royal College of Physicians of Ireland (RCPI), 2015).
- All live vaccines are generally contraindicated during pregnancy. If the patient is non-immune to an illness that requires a live vaccine e.g. measles, mumps or rubella, this should be mentioned in the GPs discharge letter and addressed post-delivery via primary care after the recommended time interval.
- Consider the effect of concurrent, recent or future medication on the effectiveness of the vaccine to be administered to the mother or the effectiveness of future vaccines for the baby e.g. immunoglobulins, immunosuppressants etc.
- If the mother has received anti-RhD immunoglobulin it is not necessary to defer MMR vaccination as the response to the vaccine is not affected (Royal College of Physicians of Ireland (RCPI), 2015).
- In some circumstances, the advice in these guidelines may differ from that in the SPC (Summary of Product Characteristics). When this occurs the advice given is based on both national and international expert opinion e.g. National Immunisation Advisory

Committee (NIAC), UK, American, Canadian, Australian and New Zealand National guidelines.

Table 1-3 illustrates current recommendations for vaccine use in pregnancy.

13.3 Table 1: Vaccines recommended in Pregnancy

Vaccine	Brand names e.g. *	Vaccine type	Use in pregnancy	Comment
Influenza	Inactivated Influenza (Split Virion) BP®	Inactivated	**YES** - routine at any stage of pregnancy	Season October to April
Pertussis, Tetanus & Diphtheria (Tdap)	Boostrix®	Inactivated Combination vaccine	**YES for every pregnancy**	Pregnant women should be offered Tdap in each pregnancy between 27-36 weeks' gestation – to protect both themselves and their infant until the primary vaccines are given. The vaccine can be given outside these times of gestation but may be less effective at providing passive protection to the infant.

The full Immunisation Guidelines for Ireland are available at http://www.hse.ie/eng/health/immunisation/hcpinfo/guidelines/

*Examples of brands used in the above table are taken from brands that are currently supplied via the HSE's cold chain service, these are liable to change depending on seasonal variation and tendering processes, see www.immunisation.ie for the complete list of brands currently distributed. Also see www.hpra.ie for the complete list of licensed vaccinations available in Ireland.

13.4 Table 2: Vaccines NOT recommended in Pregnancy

Vaccine	Brand names e.g. *	Vaccine type	Use in pregnancy	Comment
BCG (Tuberculosis)	BCG SSI brand	Live	**NO** - contraindicated	Defer until postnatal period
HPV (Human Papillomavirus)	Gardasil®	Recombinant	**NO** - contraindicated	Defer until postnatal period. Limited data
MMR (Measles, Mumps & Rubella)	Priorix® MMRVAXPRO®	Live	**NO** - contraindicated	Defer until postnatal period. At least once month before conception
Varicella (Chicken pox)	**Varivax®	Live attenuated	**No** - contraindicated	Defer until postnatal period. Allow at least 3 months after last vaccination before conception.

The full Immunisation Guidelines for Ireland are available at
http://www.hse.ie/eng/health/immunisation/hcpinfo/guidelines/
*Examples of brands used in the above table are taken from brands that are currently supplied via the HSE's cold chain service, these are liable to change depending on seasonal variation and tendering processes, see www.immunisation.ie for the complete list of brands currently distributed. Also see www.hpra.ie for the complete list of licensed vaccinations available in Ireland.
**This vaccine is not supplied by the HSE National Cold Chain Service

13.5 Table 3: Other vaccines in Pregnancy (a)

Vaccine	Brand names e.g. *	Vaccine type	Use in pregnancy	Comment
Hepatitis A**	Havrix monodose ®	Inactivated	Risk benefit analysis. Consider if high risk	UK and Canadian Guidelines state to give if clinically indicated.
Hepatitis B**	HBVAXPRO ® Engerix®	Recombinant Does not contain live vaccine	Caution limited data. Risk benefit analysis	UK and Canadian Guidelines state to give if there is definite risk of infection. Consider for high risk
Meningococcal (vs *Neisseria meningitidis*)	Menveo – MenACWY Menjugate (MenC) Bexsero (MenB) Pneumovax 23®	Conjugate	May be given when indicated	
Pneumococcal (vs *Streptococcus pneumoniae*)	Pneumovax 23®	Inactivated	May be given when indicated	UK and Canadian Guidelines say to give when the need for protection is required without delay
Polio	Available as Combination vaccines- IPV Boostrix® (Tdap/IPV) Revaxis® (Td/IPV)	Inactivated combination vaccine (IPV)	Limited data, not routinely recommended	UK, CDC, Australian and Canadian Guidelines say to give when the need for protection is required without delay

13.6 Table 3: Other Vaccines in Pregnancy (b)

Vaccine	Brand names e.g. *	Vaccine type	Use in pregnancy	Comment
Typhoid	**Typhim VI ®	Inactivated	Inadequate data for specific recommendation	UK and Canadian Guidelines state If the risk of typhoid is high, vaccination should be considered
Tetanus & Diphtheria	Dite booster® Td	Inactivated Combination vaccine	Risk benefit analysis	CDC, Australian and Canadian Guidelines says can be used if indicated
Yellow Fever	**Stamaril®	Live	Generally avoid CDC advises risk benefit analysis	UK Guidelines state, when travel is unavoidable, the risk from the disease and the theoretical risk from the vaccine have to be assessed on an individual basis.

The full Immunisation Guidelines for Ireland are available at
http://www.hse.ie/eng/health/immunisation/hcpinfo/guidelines/
*Examples of brands used in the above table are taken from brands that are currently supplied via the HSE's cold chain service, these are liable to change depending on seasonal variation and tendering processes, see www.immunisation.ie for the complete list of brands currently distributed. Also see www.hpra.ie for the complete list of licensed vaccinations available in Ireland.
**This vaccine is not supplied by the HSE National Cold Chain Service

13.7 Useful websites

American Academy of Pediatrics	USA	www.aap.org
American Medical Association	USA	www.ama-assn.org
Australian Immunisation Handbook 10th Edition	Australia	http://www.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home~handbook10part3~handbook10-3-3
Centers for Disease Control and Prevention Guideline for vaccination pregnant women	USA	http://www.cdc.gov/vaccines/pubs/preg-guide.htm
Department of Health	Ireland	www.doh.ie
Department of Health	UK	www.dh.gov/uk/greenbook
Health Protection Surveillance Centre	Ireland	www.hpsc.ie
Health Service Executive Vaccines and pregnancy 2015		http://www.hse.ie/eng/health/immunisation/pubinfo/pregvaccs/VaccPregnancy.html
HSE / Public Communicable Diseases group – Management of Pertussis	Ireland	www.hpsc.ie/A-Z/VaccinePreventable/PertussisWhoopingCough/InformationforHealthcareWorkers/File,13577,en.pdf
Health Service Executive	Ireland	www.hse.ie
HSE National Clinical Programme for Obstetrics and Gynaecology	Ireland	www.hse.ie/obsgynae
Immunization Action Coalition	USA	www.immunize.org
Immunise Australia Program	Australia	http://www.immunise.health.gov.au
National Institutes of Health	USA	www.nih.gov
National Immunisation Office	Ireland	www.immunisation.ie
National Network for Immunization Information	USA	http://www.vaccinationinformationnetwork.com/
New Zealand Immunisation Handbook	New Zealand	http://immunisation.book.health.govt.nz/4+Immunisation+of+special+groups/4.1+Pregnancy+and+lactation#4.1.2+During+pregnancy
Public Health England	UK	https://www.gov.uk/government/organisations/public-health-england
Royal College of Physicians of Ireland, National Clinical Programme for Obstetrics and Gynaecology	Ireland	https://www.rcpi.ie/faculties/obstetricians-and-gynaecologists/national-clinical-guidelines-in-obstetrics-and-gynaecology
Medical Research Council, United Kingdom	Ireland	www.mrc.ac.uk/index.htm

14 Restricted Anti-Infectives in Pregnancy

With the emergence of antimicrobial resistance it is important that antimicrobials are used in a judicious manner to ensure that we reduce the possibility of resistance emerging. It is also important to ensure that when we use either expensive or broad-spectrum antimicrobials that they are being used for the correct reason and for a specific indication.

Below is a suggested list of restricted antimicrobials and antiinfectives for maternity units. It is important that this suggested list is adapted locally to ensure compliance with the hospital's overall restriction list policy. Auditing of restricted list prescribing should be done against local standards and guidelines as opposed to these national standards which are for guidance purposes only.

Suggested list of restricted anti-infectives in pregnancy
Aciclovir intravenous use ≥48 hours
Amikacin
Anti-fungals intravenous use (e.g. liposomal amphotericin, caspofungin, anidulafungin, fluconazole)
Ciprofloxacin, moxifloxacin and levofloxacin
Daptomycin
Fidaxomicin
Ganciclovir
Gentamicin use for ≥ 3 days (risk of fetal ototoxicity)
Intravenous immunoglobulin (IVIg)
Linezolid
Meropenem use ≥48 hours

15 Research Recommendations

During the production of these guidelines, the gap in knowledge regarding the use and dosing of antimicrobials has been highlighted. Although there may be evidence behind some treatment options, there are many situations where the optimal drug or dose is not known and there is a lack of evidence base present. We have presented below research recommendations to address a knowledge gap that currently exists and will help to improve future editions of these guidelines.

1. What is the optimal dose of gentamicin in pregnancy; 5mg/kg/day in either one single dose or in three divided doses?
2. What weight should be used in the third trimester when calculating vancomycin and gentamicin doses to achieve the optimal use of the drug; booking weight, ideal weight or actual weight?
3. What is the optimal drug and dose for pyelonephritis in pregnancy?
    a. Cefotaxime high dose
    b. Ceftriaxone 1g OD
    c. Ceftriaxone 2g OD
4. What is the best regimen for pelvic inflammatory disease in pregnancy taking into account efficacy, dosing and risk of toxicity to the fetus?
5. What is the national rate of erythromycin and clindamycin resistance in Group B Streptococcus?
6. What is the best dose of gentamicin to use for C-section prophylaxis?
7. What are the pharmacokinetics and pharmacodynamics of cefuroxime and ceftriaxone in the third trimester in the setting of surgical prophylaxis and sepsis?
8. What is the best way to treat mothers who have seroconverted with respect to CMV in pregnancy?
9. What is the best way to identify, investigate and treat Candida related mastitis?
10. What is the reported incidence of penicillin allergy in pregnancy, and how does this compare to the true incidence?

11. How can we ensure that cephalosporins are safely used in patients with a history of non-immediate penicillin allergy?
12. Should azithromycin, clarithromycin or erythromycin be used for prophylaxis in PPROM? Is a β-lactam antimicrobial also required
13. Is azithromycin safe for use in all trimesters of pregnancy?

16 Implementation Strategy

- Distribution of guideline to all members of the Institute and to all maternity units.
- Distribution to the Directorate of the Acute Hospitals for dissemination through line management in all acute hospitals.
- Implementation through HSE Obstetrics and Gynaecology Programme local implementation boards.
- Distribution to other interested parties and professional bodies.

17 Qualifying Statement

These guidelines have been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. Clinical material offered in this guideline does not replace or remove clinical judgement or the professional care and duty necessary for each pregnant woman. Clinical care carried out in accordance with this guideline should be provided within the context of locally available resources and expertise.

This Guideline does not address all elements of standard practice and assumes that individual clinicians are responsible for:

- Discussing care with women in an environment that is appropriate and which enables respectful confidential discussion.
- Advising women of their choices and ensure informed consent is obtained.
- Meeting all legislative requirements and maintaining standards of professional conduct.
- Applying standard precautions and additional precautions, as necessary, when delivering care.
- Documenting all care in accordance with local and mandatory requirements.

18 List of relevant national guidelines

The full current list of Obstetrics and Gynaecology Programme Clinical guidelines are available at:

http://hse.ie/eng/about/Who/clinical/natclinprog/obsandgynaeprogramme/guidelines/guidelines/

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