Author/s:
Boast, A;Gwee, A

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Absence of evidence: antimicrobial prescribing in neonates, elderly and pregnant women

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Antimicrobial resistance has been declared by the World Health Organization a global crisis.[1] The response to this should be two-fold: 1. development of new antimicrobials 2. ensuring safe and effective use of existing antimicrobials. In this issue of *Internal Medicine Journal*, Chean *et al*[2] highlight the reluctance to prescribe gentamicin in pregnant women, despite the low rate of serious side effects. The authors emphasise the importance of *appropriate* prescribing of gentamicin in this vulnerable population, rather than complete avoidance of its use.[2] The difficulties in prescribing antimicrobials in populations where evidence is lacking, namely pregnant women, also extends to patients at the extremes of age (ie neonates and the elderly). The altered physiology (ie renal clearance, total body water) in these populations lead to challenges in dosing due to altered drug pharmacokinetics. In this editorial, we primarily focus on the issues associated with prescribing gentamicin.

There is a concerning paucity of data on dosing recommendations for antimicrobials, including gentamicin, at the extremes of age. Early phase clinical trials are designed to determine safety profile and dosage of new drugs and almost exclusively study healthy adults aged 18 to 65 years. Consequently, data from healthy adults are frequently extrapolated to guide dosing in neonates, children and older adults (aged >65 years), despite substantial physiological differences in these age groups with resultant effects on drug pharmacokinetics.[3, 4]

If children are included in clinical trials, this rarely extends to neonates. Although neonatal drug development pathways are well defined and legislation in the European Union and the United

States exist to promote paediatric clinical trials, a review in 2009 found neonates were included in only 6% of paediatric studies.[5] Consequently, neonatal drug formularies often rely on consensus to determine dosing recommendations and there is significant variability between guidelines, particularly for antibiotics.[6] Without sufficient clinical trials, paediatricians often use drugs outside the approved indications (off-label) or without marketing authorisation (unlicensed).[7] In neonates, off-label prescribing and use of unlicensed drugs, particularly antimicrobials, is common and increases the risk of medication errors, adverse drug reactions, and unpredictable drug concentrations which may result in toxic or ineffective treatment. [7, 8] Furthermore, this raises ethical issues with regard to safety monitoring and informed consent.[3] Although there are financial and ethical barriers to including neonates in clinical trials, this must be balanced against the widespread use of drugs which have not been rigorously tested in this age-group.[3]

In neonates, reduced gastric emptying results in unpredictable drug absorption, while the volume of distribution is increased due to high total body water content and reduced plasma protein binding.[9] Renal excretion of drugs is variable and increases with weight, gestational age and postnatal age.[9] Appropriate dosing of renally cleared antibiotics such as aminoglycosides, carbapenems and vancomycin is therefore particularly challenging.[9] Furthermore, drug toxicity can be difficult to identify in this age-group with potential life-long implications.

At the other end of the age-spectrum, the inclusion of elderly patients in drug trials is also generally avoided due to concerns regarding inferior treatment response, toxicity and treatment-related mortality.[10, 11] However, recent studies have shown similar survival and toxicity outcomes in early phase drug trials involving elderly patients, supporting the inclusion of this population in clinical trials.[10, 11]Various age-related changes affect drug pharmacokinetics in the elderly patients. Particularly in the frail elderly, there is a reduction in lean body weight and increase in adipose tissue, resulting in an increased half-life of lipid-soluble antimicrobials (eg rifampicin, metronidazole).[12] In addition, total body water is reduced, increasing the concentration of water-soluble antimicrobials (eg gentamicin, vancomycin), while a decrease in albumin results in increased free concentrations of acidic antimicrobials (eg penicillin, ceftriaxone).[12] Age-related kidney impairment increases the half-life of water-soluble antimicrobials and inadequate renal dose adjustment is a frequent error when prescribing antimicrobials in elderly patients, particularly with cephalosporins and gentamicin.[13, 14] There is also a greater risk of drug-interactions due to the higher rate of polypharmacy with increased adverse drug reactions.[14] Although dosing guidelines include renal dose adjustment, for most drugs, standard drug formularies do not include dosing guidelines specifically targeted to elderly patients.

Chean *et al*[2] highlight the underutilisation of gentamicin for Gram-negative infections in pregnant women. Gentamicin is an aminoglycoside antibiotic with rapid bactericidal action and resistance is rare, even with multi-drug resistant organisms. In neonates, gentamicin is

commonly prescribed for the empirical treatment of sepsis.[15] Despite its frequent use, data are lacking on the optimal dosing regimen of gentamicin in this age group, and moreover, the target peak and trough concentrations.[15] This is reflected by the interinstitutional variation in therapeutic drug monitoring protocols both nationally and internationally.[16] Although the peak level of gentamicin correlates with efficacy,[17] few units monitor peak levels even in the setting of Gram-negative sepsis.[16] Furthermore, trough concentrations less than 1-2 mg/L are standard of care to reduce the risk of nephrotoxicity, however this is based on adult data from 30 years ago.[18, 19]

Gentamicin is frequently avoided in elderly patients due to concerns regarding ototoxicity and renal toxicity.[20] There are no specific guidelines on appropriate gentamicin use in the elderly population, although the Therapeutic Guidelines recommend avoidance in 'advanced age' (eg 80 years or older), depending on calculated renal function'.[21] Of note, gentamicin has a significantly lower clearance in the frail elderly compared to non-frail elderly and lean bodyweight should be used to estimate creatinine clearance.[22] Increasing age is a risk for developing gentamicin induced nephrotoxicity due to pre-existing renal impairment and prescription of concomitant nephrotoxins.[23] Although there is evidence to suggest that courses lasting longer than one week are associated with an increased rate of nephrotoxicity in adults aged 70 years or older,[24] there are no data on the prevalence of nephrotoxicity in elderly patients treated with short courses of appropriate renally-adjusted doses of gentamicin.

It is ironic that data on antimicrobial dosing are lacking in the most vulnerable of populations ie neonates, pregnant women and elderly patients. With emerging antimicrobial resistance, there is an urgent need for pharmacokinetic and safety data for existing antimicrobials to optimise current dosing and therapeutic drug monitoring regimens. Furthermore, in the development of new antimicrobials, drug trials must be extended to include neonates and elderly patients. However, the ethical and financial limitations around trials in these populations is likely to be enduring. While opportunistic pharmacokinetic studies using population pharmacokinetic modelling may enable further establishment of evidence based dosing guidelines, clinical validation is still required. The drive for improvement in safe and effective prescribing in these patient groups needs to be led by government through financial incentives to drug companies and investigators.

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Authors: Alison Boast MD[1], Amanda Gwee MBBS[1,2,3]

Affiliations:

[1] Infectious Diseases Unit, Department of General Medicine, The Royal Children's Hospital, Parkville, Victoria, Australia.

[2] Department of Paediatrics, The University of Melbourne, Parkville, Victoria, Australia.

[3] Murdoch Children's Research Institute, Parkville, Victoria, Australia.

Corresponding Author: Dr Amanda Gwee. Department of General Medicine. The Royal Children's Hospital Melbourne. 50 Flemington Rd Parkville VIC 3052 Australia. Tel +61 (3) 9345 5522 Fax: +61(3) 9345 4751

Email: amanda.gwee@rch.org.au

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