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REVIEW

Antimicrobial Stewardship in the Frail Elderly

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Abstract

Antimicrobial therapy is essential to modern healthcare practice. However, years of injudicious use has contributed to the development of population and individual level harm from antimicrobial resistance. The frail elderly are particularly at risk from infection as well as antimicrobial adverse effects due to multimorbidity, polypharmacy and declining physiological reserve. Diagnosis and management decision making may be challenging in this vulnerable group due to subtle or absent symptoms and signs. Antimicrobial stewardship is the systematic approach to safe and effective use of antimicrobials to optimise outcomes, minimise harm and preserve future therapies. Herein, we consider the significance and importance of antimicrobial stewardship in the frail elderly and suggest ten steps to assist clinicians in the recognition, investigation and management of infection in this group.

Key words: infection; frailty; elderly; antimicrobial stewardship; antimicrobial resistance

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Introduction

Antimicrobials are the cornerstone of modern medicine, making communicable disease survivable, preventing life-threatening complications of surgery and enabling cancer and immunomodulatory therapies. Decades of injudicious use including unnecessarily broad spectrum antibiotics, overly long durations of therapy in common bacterial infections, unnecessary use in viral infections and over use of the intravenous (IV) route, have been important factors in driving antimicrobial resistant infections (Murray et al, 2022), as well as other antimicrobial related adverse events including *Clostridiodes difficile* (Keller and Surawicz, 2014). To allow clinicians to manage complex infections now and to preserve therapies for the future, it is imperative we treat antimicrobials with great care and practice the principles of antimicrobial stewardship.

Antimicrobial resistance (AMR) is a major, global, public health threat. An estimated 4.9 million AMR related deaths each year (WHO, 2022a) worldwide are projected to increase to at least 10 million by 2050 (O'Neil, 2016). Vulnerable populations—the young, the old and particularly those living in low-income settings—carry the highest burden. Consequently, AMR is one of the World Health Organisation's top 10 priorities (WHO, 2021).

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Resistance to antibiotics is an ancient and naturally occurring phenomenon. However, the risk of AMR is accelerated when antibiotics are misused and particularly when populations of bacteria are exposed to sub-lethal antibiotic concentrations. This is demonstrated most starkly in critical care settings, where pan-resistant pathogens are increasingly recognised (Mancuso et al, 2021). Factors driving AMR and the solutions to minimising further harm are complex and multifactorial and require a comprehensive "one health" approach across human, animal and environmental sectors.

Infection presents a significant challenge for the frail elderly who are particularly vulnerable due to comorbidity, polypharmacy, declining functional ability and a lack of physiological reserve (Laupland, 2022). Frailty is strongly associated with prolonged courses of antibiotics, longer hospital stays and increased mortality (Zhao et al, 2023), with a quarter of elderly patients dying within a month of contracting a multidrug resistant infection (UK Health Security Agency, 2023).

The following article provides a viewpoint on contemporary practice. We consider the significance and importance of antimicrobial stewardship in frailty and suggest ten steps (summarised in Table 1) to assist in the recognition, investigation and management of infections in the frail elderly.

The Importance of Antimicrobial Stewardship

Antimicrobial stewardship (AMS) describes the systematic approach to ensure safe and effective use of antimicrobials to optimise outcomes, minimise harm and preserve future therapies. AMS, like effective hand hygiene, needs to be ingrained in and fundamental to everyday clinical practice. The World Health Organisation has produced the AWaRe (Access, Watch, Reserve) classification (WHO, 2022b), a global tool to empower stewardship by providing prescribing targets that encourage the use of first or second line therapies, emphasising the importance of reserving 'last resort' antibiotics for the treatment of complex drug resistant infections.

Antimicrobials are associated with other risks in addition to AMR. At least one in five hospital patients suffer an antibiotic associated adverse event which alters their clinical journey (Tamma et al, 2017). Most commonly these are gastrointestinal effects and haematological or renal toxicity. The use of broader spectrum agents, in particular cephalosporins, beta-lactam/beta-lactamase inhibitor combinations, clindamycin and fluoroquinolone antibiotics are significantly associated with *Clostridioides difficile* infection (Teng et al, 2019). Unnecessarily prolonging intravenous (IV) antibiotic therapy (or failure to switch in a timely manner from IV to oral therapy) risks device-related infections including skin and soft tissue infections and *Staphylococcus aureus* bacteraemia. Time spent reconstituting and administering IV therapy reduces opportunities for other essential nursing tasks. AMS should be a priority for everyone, regardless of profession, speciality or grade. Antimicrobial stewardship is effectively everyone's business.

Table 1. Ten steps to guide antimicrobial stewardship.

1	Prompt recognition, investigation and management of sepsis ● Delayed presentation, loss of physiological reserve and relative immunosenescence leads to worse outcomes from sepsis in the elderly ● Blood cultures are a key investigation. Send 2 sets (4 bottles) fully filled prior to antibiotic therapy
2	Avoid unnecessary investigations ● Urine dips are unreliable in woman over 65. Only send urine for culture if there are symptoms of a urinary infection ● Urinary catheter bags are colonised with bacteria and so urine samples are not reliable at diagnosing infection
3	Treat the patient, not the result ● Wound swabs will grow colonising bacteria and in the absence of signs of infection (cellulitis, purulent discharge) do not require treatment ● Do not treat asymptomatic bacteriuria
4	Many infections will get better without antibiotics ● Drain pus, change catheters and be aware of infection mimics like venous eczema ● Mild lower respiratory tract infections without purulent sputum are likely to improve without antibiotics
5	Local (non-antibiotics) measures are important ● Source control is key in managing infection: remove pus where possible, debride ulcers and remove infected prosthetic material ● Staying hydrated, nourished and mobile is particularly important for the frail elderly
6	Follow local infection management guidance ● Following antibiotic guidelines saves lives and reduces risks of adverse events and other complications ● Use of co-amoxiclav, clindamycin, ciprofloxacin and cephalosporins should be minimised in the elderly unless no suitable alternatives, due to the risk of *Clostridiodes difficile*
7	Take a proper antibiotic allergy history ● The majority of self-reported, historical penicillin allergies (particularly in the elderly) are not true allergies and should be carefully assessed ● Interrogate penicillin allergy histories at every opportunity and consider if it is safe to de-label the allergy if there is a low probability of a Type I or Type IV hypersensitivity reaction
8	Review prescription rationale and duration regularly ● Documenting the rationale for antibiotic prescribing helps others decide on IVOST (intravenous to oral switch therapy) timing or antibiotic duration later in the patient journey ● Review antibiotic prescriptions on every ward round and clinical review
9	Shorter is better ● Multi-centre randomised controlled trials demonstrate that shorter courses of antibiotics and early IVOST are non-inferior to long courses of intravenous (IV) therapy ● Oral antibiotics spare vascular device related complications and reduce the valuable time required to reconstitute and administer IV antibiotics
10	Value and support the broader team ● All healthcare professionals, regardless of role or seniority, should be aware of antimicrobial stewardship principles and their role in safe guarding antibiotic use ● Antimicrobial stewardship is everyone's business

Frailty and Risk of Antibiotic Harm

Antimicrobial stewardship is of particular importance in the frail elderly. Frailty is a complex state where over time, body systems become less resilient to stress (British Geriatrics Society, 2018). In the UK, up to 25% of those over the age of 85 are classified as "frail" (Sinclair et al, 2022) and as the elderly population is projected to increase by 4 million people over the next 15 years (Government Office for Science, 2016) frailty will become more prevalent. In this context it is inevitable that antibiotic and hospital environment exposure will increase with subsequent increase in risk of resistant infections.

Compared to the majority of the population, infection in the frail elderly can present with subtle or absent symptoms and signs, making diagnosis significantly more challenging. Patients may only complain of weakness or delirium, fever may be absent and the typical biochemical response may be blunted (Hosty et al, 2021; Podnos et al, 2002).

When treating infection, the frail elderly are more vulnerable to adverse drug reactions (Woodford and Fisher, 2019) and they are often excluded from clinical trials, meaning the pharmacodynamics and kinetics of antibiotics are less well understood. It is not normal practice to routinely correct drug doses for age or for reduced liver mass and hepatic blood flow which is seen in healthy ageing and which may cause reduced first pass metabolism or drug clearance. It is also challenging to measure renal function in people with sarcopenia (Davies and O'Mahony, 2015). *Clostridioides difficile* infection is a well-recognised consequence of antibiotic prescribing in the frail elderly and the consequences include organ failure, recurrent infection and death (Keller and Surawicz, 2014), emphasising the importance of minimising harm at the outset by avoiding unnecessary and overly broad spectrum antibiotic prescribing.

Those who are frail are significantly less likely to be suitable for curative surgery, for example, to drain an intra-abdominal collection, remove an infected pacemaker or prosthetic hip. This leads to suboptimal treatment and potentially long term suppressive antibiotic courses (Kiss et al, 2022). Outpatient or ambulatory management is often less accessible (Oliver and Skalweit, 2023) and so the frail elderly are likely to remain inpatients on IV antibiotics for longer, with the potential for associated cannula complications and further deconditioning.

Managing Infection at the End of Life

A specific consideration for the management of infection in the frail elderly is infection at the end of life. This is a common scenario and often the final clinical event which leads to death. While antimicrobials may reduce microbial load and be used with the intent to alleviate pain, they can exacerbate symptom burden and potentially prolong dying and suffering. Recognition of end of life and dying is challenging and clinicians must manage the complexity of judging the stage of decline and whether it is appropriate to attempt to reverse infection driven decline. In an unpublished Public Health Scotland (PHS) survey conducted as part of a Scottish Antimicrobial Prescribing Group (SAPG) short life working group, a significant in-

crease in community antibiotic prescribing in the last 5 days of life was observed between 2011 and 2018 (PHS, personal communication). Whilst this may reflect increasing end of life care at home, it highlights the importance of advanced care planning and anticipatory care approaches at the end of life. Managing infection at the end of life requires a careful assessment of the relative contribution of infection to symptom burden and understanding the patient and carer's priorities in regard to both quality and quantity of life. A nuanced, personalised approach, making shared decisions with the patient and family about future care is essential. Ideally, if antimicrobials are prescribed, they should be reviewed regularly (daily if IV) with an assessment of response with these principles in mind. A recent SAPG scoping review provides good practice recommendations to guide those caring for people at the end of their life (Scottish Antimicrobial Prescribing Group, 2020; Seaton et al, 2021).

Ten Steps to Guide Antimicrobial Stewardship

Prompt Recognition, Investigation and Management of Sepsis

'Sepsis' describes the syndrome of end organ dysfunction due to a dysregulated immune response to infection. It is estimated that every hour delay in treating with antibiotics is associated with a 4% increase in mortality (Seymour et al, 2017). Delayed presentation, loss of physiological reserve and relative immunosenescence leads to worse outcomes in the elderly (Podnos et al, 2002). Common sources of infection are respiratory or renal tract, skin and soft tissue (including pressure ulcers) and intra-abdominal or intra-pelvic. Other sources of infection which may be less obvious include bone and joint, endocarditis and infected prosthetic material. Where there is clinical uncertainty, a collateral history from family or care providers may be extremely useful. Blood cultures are essential, even in afebrile patients and ideally before the administration of antibiotics. As the likelihood of detecting bacteraemia is directly correlated to the volume of blood drawn, it is strongly recommended to obtain at least 10 mLs of blood into each blood culture bottle and to obtain a total of two sets of cultures (four bottles) (NHS England, 2023). Optimising blood culture yield allows therapy to be targeted to a specific organism and resistance profile and organism identification often helps in identifying the source of infection.

Avoid Unnecessary Investigations

Judicious, targeted investigations minimise the risk of misleading results or the compulsion to treat an organism grown in a sample 'just in case'. It is not appropriate to submit a urine for microbiological testing in the absence of urinary symptoms and treatment of asymptomatic bacteriuria in the elderly is absolutely not recommended. It is well recognised that bacteria frequently colonise the lower genital tract of women over 65 years old, so urine dipstick testing, irrespective of symptoms, is unreliable and is not advised (Scottish Antimicrobial Prescribing Group, 2021a). A clean catch urine can be difficult to achieve in an incontinent patient, so sampling with an aseptically placed in/out catheter may be required to

prevent contamination from faecal or perineal flora. If urinary catheter associated infection is suspected, investigate with as clean a catch urine as possible, flowing from the catheter tubing rather than from the catheter bag where bacteria commonly colonise. Superficial wound swabs of lower limbs and feet will grow organisms that colonise wounds and in the absence of inflammation or pus they cannot be judged to be pathogenic or require treatment. This is particularly true for Gram negative or anaerobic organisms and in general, empirical therapy should not be altered in response to these results, especially if a wound infection is improving.

In a patient suspected to have an infection, blood cultures are always appropriate. Bacteraemia may be present without fever or clear features of sepsis—particularly so in the elderly patient.

Treat the Patient, not the Result

Skin, mucous membranes, the gastrointestinal tract and airways are colonised by many billions of bacteria, forming the human microbiome. There is growing evidence of the microbiome's role in the maintenance of many aspects of health as well as the potential harm or "microbiotoxicity" following its disruption by antibiotics (Theodosiou et al, 2023). It is therefore expected that bacteria will grow from samples from non-sterile sites. Laboratories will often report results as 'no significant growth', indicating the organisms cultured reflect what is expected to be there. Urine is easily contaminated and consequently, asymptomatic bacteriuria does not require treatment, particularly from a catheter sample (Scottish Antimicrobial Prescribing Group, 2021a). There are many causes for raised inflammatory markers that will not be reversed with antibiotics, for example; viral infections, rheumatological conditions, ischaemia/infarction and malignancy. As CRP (C reactive protein) has a half-life of roughly 19 hours (Markanday, 2015), levels take time to normalise and patients usually improve clinically before the CRP improves. A falling CRP or a CRP at a specific value is not needed to guide intravenous to oral switch therapy (IVOST) decisions or antibiotic stop dates.

Many Infections will Get Better without Antibiotics

Many mild infections will improve without antibiotics. Superficial boils and ingrown toenails are likely to settle with draining pus and mild respiratory infections in the community can be self-limiting (Little et al, 2013). Importantly, skin that initially appears infected may be inflamed for non-infective reasons and will be better managed with compression bandaging and tissue viability input or vascular intervention for lymphoedema, venous eczema and sloughy leg ulcers.

Local (Non-Antibiotic) Measures are Important

Antibiotics are not a substitute for cleaning wounds thoroughly, managing ulcers with pressure relief, debridement, appropriate dressings and footwear and removing pus by draining abscesses. Removing any infected prosthetic material where possible is key, as residual plastic or metal remains a nidus of infection, allowing bacteria to develop biofilm which is extremely difficult to eradicate.

It is particularly important for the frail elderly with infection to stay hydrated, nourished and mobile to maintain physiological reserve. Involvement of the family and carers and in hospital the wider multi-disciplinary team is key.

Follow Local Infection Management Guidance

Mortality is reduced when prescribers adhere to empirical antimicrobial guidelines. In a review of 145 stewardship studies, Schuts et al (2016) found that following guidelines led to a relative risk reduction in mortality of 35%, and no detrimental effect was seen with IVOST or de-escalation of antibiotics. Local infection management guidelines should consider local resistance patterns (antibiograms) and the prevalent organisms within common presentations, as well as common side effects and drug-drug interactions, which are particularly relevant in the multi-morbid, frail patient. Important drug interactions include doxycycline and ciprofloxacin interaction with cations (iron, magnesium, calcium as tablets or in supplement drinks) which leads to reduced antibiotic absorption. Cations should be administration at least 2 hours prior to or following doxycycline or quinolone antibiotics (Eljaaly et al, 2021). As doxycycline undergoes enterohepatic recirculation, it cannot be co-prescribed with iron, so iron should be suspended for the course rather than separated. Co-amoxiclav, clindamycin, ciprofloxacin and cephalosporins are associated with increase rates of *Clostridiodes difficile* so should be avoided in the elderly unless there are no suitable alternatives (Teng et al, 2019). Recent MRHA (Medicines and Healthcare products Regulatory Agency) guidance emphasises that prescribers have a duty of care to avoid fluoroquinolones if other alternatives are available, as toxicities can be disabling and life threatening (Medicines and Healthcare products Regulatory Agency, 2024). However, it is important to note that fluoroquinolones may be the only available oral option for some resistant Gram negative infections and their use may avoid unnecessary escalation of therapy to broader spectrum intravenous agents which may be associated with other harms.

Take a Proper Antibiotic Allergy History

Co-trimoxazole, fluoroquinolones, tetracyclines or meropenem are often used as second line antibiotics when treating a patient with a history of suspected penicillin allergy. Common side effects, drug interactions and AMR risk could be avoided if those patients without a true penicillin allergy could be reliably identified and receive a penicillin antibiotic. In a study of 998 patients with suspected b-lactam allergy, Co Minh et al (2006) found that only 1 in 10 people were truly allergic. In the context of true allergy, 80% of people lose sensitivity to penicillin after 10 years (Blanca et al, 1999). Ideally, any history of a potential penicillin allergy should be fully interrogated, not just accepted. If a reaction is mild and clearly not an allergy (for example, nausea, vomiting or diarrhoea), then clinicians can feel confident to de-label and treat with penicillin. If the reaction is potentially IgE mediated (for example, a rash) but is historic or mild, then it may be safe to challenge with a penicillin under controlled observation. The Scottish Antimicrobial Prescribing Group have developed a penicillin allergy de-labelling tool kit for

use by non-allergists in hospital and following local clinical governance processes (Sneddon et al, 2021; Scottish Antimicrobial Prescribing Group, 2021b).

Review Prescription Rationale and Duration Regularly

Antimicrobial prescribing is a dynamic process and prescriptions should be reviewed each day to consider appropriateness for IVOST, de-escalation or discontinuation of antibiotics. Documenting the rationale for starting antibiotics aids those seeing patients later in their journey to stop the antibiotic if the diagnosis changes. With a few caveats (notably *Staphylococcus aureus* bacteraemia), if there is clinical improvement, uncomplicated infection and the patient is able to take orally bioavailable antibiotics suitable for the infection source, then IVOST is usually appropriate.

Shorter is Better

Safe, appropriate IVOST reduces the amount of time a patient spends receiving IV antibiotics, reducing the opportunity for cannula associated hospital acquired infections and reducing the time spend preparing and administering IV antibiotics. There is increasing evidence of non-inferiority of early IVOST and shorter courses of antibiotics across a range of pathologies. The oral versus intravenous antibiotics for bone and joint infection (OVIVA) trial showed switching to oral antibiotics after 7 days of IV antibiotics was safe in bone and joint infection (Li et al, 2019). The partial oral treatment of endocarditis trial (POET) similarly showed non-inferiority of oral therapy after at least 10 days of intravenous antibiotics to treat left sided endocarditis (Iversen et al, 2019). Data demonstrates 7 days is safe to treat most Gram negative bacteraemia (Yahav et al, 2019) and 3 days can be non-inferior to a week for treatment of community acquired pneumonia (Dinh et al, 2021). Clinical trial outcomes investigating earlier IV to oral switch in uncomplicated *Staphylococcus aureus* bacteraemia are awaited.

Value and Support the Broader Team

Antimicrobial stewardship is not the sole responsibility of the medical prescriber. All staff involved in the care of patients should feel empowered to be involved with AMS. Good AMS starts with the recognition of the presence and severity of infection and the arranging of appropriate investigations. Training grade doctors are the primary prescribers in hospitals so they should be encouraged to record treatment decisions and proposed durations of therapy and not routinely defer IVOST decisions or stopping antibiotics to consultant ward rounds. Nursing staff are ideally positioned to observe and document clinical improvement or deterioration and as such are vital in informing and prompting clinical decision making around escalation or de-escalation of therapy. This includes encouraging the oral route and documentation of proposed duration of therapy. Increasingly, in both primary and secondary care, nurses, pharmacists and podiatrists as well as other non-medical healthcare professionals are prescribing and it is vital the same AMS principles are encouraged in these groups. Clinical pharmacy has a vital role in safe medicines management and increasingly in treating common ailments and manag-

ing polypharmacy in primary care. Specialist antimicrobial pharmacists have a central organisational role in institutional antimicrobial stewardship programmes as well as in individual patient care.

Conclusion

The frail elderly are at great risk of harm from both infection and antimicrobials. However, there is significant potential for reducing harm with astute diagnoses and prompt, appropriate treatment. These 'ten steps' can be used to guide the management of infection in this cohort.

Key Points

- The frail elderly are at particular risk of death from infection and may present non-specifically, making diagnosis and identification of a source of infection challenging.
- Antimicrobial stewardship is the systematic approach to ensuring safe and effective use of antimicrobials to optimise outcomes, minimise harm and preserve future therapies.
- Prompt identification of infection, appropriate investigation and targeted treatment when it is required is essential for good antimicrobial stewardship.
- Avoiding unnecessary investigations, carefully interpreting laboratory results and individualising decision making is essential for safe and appropriate patient care.
- Antimicrobial treatment at the end of life, may exacerbate symptom burden and suffering and treatment decisions should be patient centred, pragmatic and shared with patients and relatives. The aim should be to minimise suffering and not to delay dying.
- Antimicrobial stewardship is the responsibility of all who care for patients, regardless of role or grade.

Availability of Data and Materials

Not applicable.

Author Contributions

CW contributed to literature review and manuscript draft and editing. Both CW and RAS made substantial contributions to the conception or design of the work. RAS made contribution to manuscript draft and editing. Both authors contributed to important editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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