National Institute for Health and Clinical Excellence

Neutropenic Sepsis
Stakeholder Comments

Please enter the name of your registered stakeholder organisation below. **NICE is unable to accept comments from non-registered organisation or individuals. If you wish your comments to be considered please register via the NICE website or contact the registered stakeholder organisation that most closely represents your interests and pass your comments to them.**				
Stakeholder Organisation:	Royal Pharmaceutical Society			
Name of commentator:	Ruth Wakeman, Head of Professional Support, Royal Pharmaceutical Society This response was prepared by the British Oncology Pharmacy Association (BOPA). In addition the RPS wishes to support the comments made by the Neonatal and Paediatric Pharmacists Group in their response to the consultation.			
Order number *(For internal use only)*	**Document** Indicate if you are referring to the **Full** version or the **Appendices**	**Page Number** **Number only** (do not write the word 'page/pg'). Alternatively write **'general'** if your comment relates to the whole document.	**Line Number** **Number only** (do not write the word 'line'). See example in cell below	**Comments** **Please insert each new comment in a new row.** **Please do not paste other tables into this table, as your comments could get lost – type directly into this table.**
Example	Full	16	45	Our comments are as follows ……
Proformas that are not correctly submitted as detailed in the line above may be returned to you				
1	Full	General		Our overarching comment is concern that the membership of the Guideline Development Group (GDG) did not include a cancer and/or anti-microbial pharmacist. • Cancer pharmacists in many cancer centres are heavily involved in, if not leading, the development of guidelines on both the prophylaxis and treatment of neutropenic sepsis and the use of GCSF. We believe that the GDG having this practical experience on the group would have allowed the guidance to be more realistic and practically useful. • As for the value of an antimicrobial pharmacist to the GDG, this has already been recognised more broadly in previous Department of Health (DH) and Health Protection Agency (HPA) guidance[i] which

				states that “all trusts should establish an Antimicrobial Management Team (AMT) or equivalent. This should consist of an antimicrobial pharmacist, a consultant microbiologist or infectious diseases specialist, and an information technology specialist. Antimicrobial pharmacists have a valuable role in AMTs and PCTs……”.
2	Full	General		We believe that the scope for this guidance in relation to the use of G(M)CSF was wrong from the beginning and the resulting draft guidance is clearly flawed as a result. The issues are: - The review of G(M)CSF only considers “survival during anti-cancer treatment” and does not consider any survival advantage for giving G(M)CSF for maintaining dose intensity which is the key reason for its use in many patients. - The review considers giving G(M)CSF to all. All international guidelines we can find[ii,iii,iv] do not recommend using G(M)CSF in this way and recommend use on the basis of risk of febrile neutropenia. Therefore there is no assessment of the point at which G(M)CSF may becomes cost effective based on the risk of febrile neutropenia. - GCSF is available to the NHS at contract price(s) that are **significantly** lower than the NHS list price. We realise the GDG was limited in its scope, and that it recognised that this period “may be too short to adequately assess the benefits of G(M)CSF use in encouraging clinicians to proceed in treatments with greater dose intensity.”. They also recognised that “clinicians in some settings are able to source G(M)CSF products at substantially reduced prices which could potentially make its use cost-effective”. The GDG clearly tried to make the best of a bad situation by making the following statement “Balancing these elements of uncertainty against the high ICER described by the economic model led to a strong decision not to recommend the use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis but also not to recommend that the use of these agents for other indications is discontinued.” Our key concern is that despite this statement, in the current financial climate, commissioners may take the detailed review of the evidence and the extremely high ICER for G(M)-CSF in the prevention of neutropenic sepsis in the absence of any similarly detailed review of its potential benefits in maintaining dose intensity as a reason to decommission the use of G(M)CSF. Therefore we firmly believe that the scope of this guidance should be increased to also cover the use of G(M)CSF in increasing dose intensity.

3	Full	5		**Recommendation on the use of quinolone prophylaxis**. The evidence for the proposed benefits of quinolone prophylaxis is disputed by some microbiologists but more importantly we are now living in the era of C. Difficile 027 (CDI) which is a potentially life-threatening infection. Use of antibacterial prophylaxis may promote the development of bacterial resistance and the risk of superinfection with organisms including methicillin resistant S. aureus and CDI. There have been well documented outbreaks of CDI in North America and in the UK at Stoke Mandeville Hospital, Maidstone & Tunbridge Wells NHS Trust and others. There are several hospitals in our region which had excellent records vis-à-vis CDI and have witnessed 027-related deaths. The associated targets for reducing CDI in NHS Trusts could be thrown off track by increased use of quinolones. The DH and HPA produced guidance in 2008 that states: "Restrictive antibiotic guidelines should be developed by trusts, through the AMT, stressing the following recommendations: • Use narrow-spectrum agents for empirical treatment where appropriate. • Avoid use of clindamycin and second- and third-generation cephalosporins, especially in the elderly. • **Minimise use of fluoroquinolones**, carbapenems and prolonged courses of aminopenicillins." The DH and HPA's recommendations on fluoroquinolones was a grade B recommendation ie strongly recommended and supported by non-RCT studies and/or by clinical governance reports and/or the Code. As such we would suggest that the recommendation that "all adult patients (aged 18 years and older) with acute leukaemias, stem cell transplants or **solid tumours**" are offered prophylaxis with a quinolone is discussed and agreed with the Healthcare Associated Infection and Antimicrobial Resistance Group at DH, with the HPA and with the wider microbiology community.
4	Full	general		**Alternative methods of neutropenic sepsis prevention** There are other methods of protecting patients from neutropenic sepsis but everything in the draft guidance centres around prophylaxis. Should diet, for example, be discussed?
5	Full	158		**Recommendation to switch from IV to oral antibiotic therapy after 48 hours of treatment in patients whose risk of developing septic**

				complications has been re-assessed as low by a healthcare professional with recognised professional competence in managing complications of anti-cancer treatment using a validated risk scoring system. The GDG do not recommend which oral treatment to use but it is our understanding that the quinolones would be most useful in this respect. There are two issues here: the issue of CDI covered in the section under order number 3; and the fact that if a patient develops a breakthrough bacteraemia while on quinolone prophylaxis, it's not beyond the bounds of probability that the isolate will be quinolone resistant. In this scenario guidance would be required. We also have concerns with the referenced validated scoring system. We feel that MASCC criteria are very complex particularly for those areas which have not used them previously. We are also aware they were derived in order to assess suitability for, amongst other things, oral treatment in an era (published in 2000) when quinolone resistance was much lower than it is now and there was no 027 CDI.
6	Full	133		**Recommendation for piperacillin-tazobactam monotherapy as standard empiric therapy** The guidance lacks any recommendations for the treatment of those patients who have a type 1 beta-lactam hypersensitivity. This is a common occurance in practice and requires guidance. This recommendation also ignores the huge rise in Extended Spectrum Beta-Lactamase (ESBL) producing coliforms over the last few years. ESBL are resistant to the actions of penicillin/beta lactamase combinations such as Tazocin. In addition, and supporting order number 3, prior quinolone use is also a risk factor for subsequent ESBL infection. Whilst the recommendation also states “unless there are local microbiological contraindications” we again feel this recommendation requires discussion and agreement with the Healthcare Associated Infection and Antimicrobial Resistance Group at Department of Health, with the HPA and with the wider microbiology community.
7	Full	137		**Recommendation for empiric glycopeptides for the initial empiric treatment of suspected neutropenic sepsis** We believe that the recommendation to “not offer empiric glycopeptides antibiotics to patients with neutropenic sepsis who have a central venous access devices" requires qualification. We would suggest this can be achieved by adding "routinely". There may be some situations, for example when treating a known MRSA carrier or someone with previous episodes of MRSA infection were initial empiric treatment may

				reasonably involve vancomycin or teicoplanin.
8	Full	58		**Recommendation to include in the initial clinical assessment of patients with suspected neutropenic sepsis**: **lactate** The recommendation with regards lactate surprised us. Practically we would question the value of this for all patients as we would suspect that we would treat someone with antibiotics if they had a high temperature and neutropenia even if they had a normal lactate.
9	Full	general		In addition to this response the RPS wishes to support the comments made by the Neonatal and Paediatric Pharmacists Group in their response to the consultation.
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Please add extra rows as needed

Please email this form to: neutropeniasepsis@nice.org.uk

Closing date: 5pm on 28.03.12

PLEASE NOTE: The Institute reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion or the Institute, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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[i] The Health Act 2006: Code of practice for the prevention and control of healthcare associated infections (Department of Health, 2008a)

[ii] Aapro et al. 2010 Update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer 47 (2001): 8 – 32

[iii] Smith et al. 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. J Clin Oncol July 1 2006; 24 (19): 3187 – 3205

[iv] National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (2011). Myeloid Growth Factors. V.I.2011