Faculty of Pharmaceutical Medicine comments and submission to DHSC call for information and evidence regarding management of Sepsis and Coroner Prevention of Future Deaths Reports

*25.6.21*

1. About the Faculty of Pharmaceutical Medicine

The Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians of the UK (FPM) ([www.fpm.org.uk](http://www.fpm.org.uk)) is a charity and professional membership body. Our mission is to advance the science and practice of pharmaceutical medicine by working to develop and maintain competence, ethics and integrity and the highest professional standards in the specialty for the benefit of the public. We set the highest scientific and ethical standards to help unlock the full potential of new medicines and make sure they are as safe as possible for patients.

FPM provides a collective voice for our 1,500 members who work to advance the research and development of new medicines to help prevent and overcome diseases that impact on the lives of patients worldwide. They are all medically-qualified and employed within the pharmaceutical and biotech industries, research organisations, drug regulatory authorities, or working as independent consultants.

# Guidance for the recognition and treatment of sepsis may be in need of expedited revision with protocols reflecting up to date NICE guidelines.

*“Sepsis guidance relating to different age groups including children and babies (i.e., to ensure it reflects NICE guidance);”*

*“The messaging about the timely and prompt prescribing of antibiotic medication is in need of a review, as the Inquest highlighted issues of a possible overly cautious approach in their use, when there was no impediment to such use, and they may have saved Sheldon’s life.”*

Sepsis is incredibly common, but the diagnosis and treatment of sepsis is controversial and confusing. It is often compounded by a misunderstanding of stewardship.

## Sepsis is difficult to define and not one disease –

*Not all Sepsis is the same (and a lot of ‘sepsis’ may not be sepsis)*

“The sepsis illness concept is predicated on infection as its trigger, acknowledging the current challenges in the microbiological identification of infection.” Singer et al 2016 (Singer, Deutschman et al. 2016)

“Up to 40% of patients initially treated for sepsis have a low post hoc probability of bacterial infection; hence, a forced rush to treatment will expose many patients to the risks of antibiotics without any benefit.” (Rhee, Chiotos et al. 2021).

The paper lists many conditions that can mimic sepsis. A paper from Mark Bonten’s group evaluated the plausibility of infection (none, possible, probable, definite) in sepsis, using available clinical, microbiological, and radiological evidence and according to the Centers for Disease Control and Prevention (CDC) and the International Sepsis Forum (ISF) criteria. On that basis, of 2579 Dutch patients treated for sepsis, 13% had a post-hoc infection likelihood of “none”, and an additional 30% of “possible”. (Klein Klouwenberg, Cremer et al. 2015). Inevitably most evidence comes from critical care units.

*Not all patients are the same*

A high percentage of patients with sepsis have marked underlying co-morbidities and make interpretation of research especially all-cause mortality extremely challenging. Most data is from critical care, either HDUs or ICUs, but has been suggested the source of 70% of sepsis is from community acquired infections (Esteban, Frutos-Vivar et al. 2007).

Diagnosis and identification of a putative bacterial pathogen will be different in different settings.

**Bacterial aetiology and antibiotic prescribing**

As 97% of patients with sepsis have possible, probable, or definite bacterial infection, choice of antibiotic both to treat individual patients and to avoid increasing in resistance due to local overprescribing is important.

*Not all antibiotics are the same*

The choice of antibiotics is substantial illustrated by WHOs AWaRE list

WHO have suggested that a classification of antibiotics as Access, Watch and Reserve as part of their Essential Medicines classification. This has been adapted for the UK (Budd 2019) to guide the use of preferred first line antibiotics (access) or those broad spectrum with higher resistance potential (watch) or those that we should use a last-line agents where there are no other option (reserve). The UK AMR National Action Plan has set targets to reduce the consumption of antibacterials in the watch and reserve groups by 10%. Most antibiotics have an IV formulation and can be used in hospital settings.

|  |  |  |
| --- | --- | --- |
| **Access** | **Watch** | **Reserve** |
| Amoxicillin / ampicillin  Penicillin – all forms  Co-trimoxazole  Doxycycline  Flucloxacillin  Fosfomycin oral  Fusidate  Gentamicin  Metronidazole  Nitrofurantoin  Pivmecillinam  Tetracycline  Trimethoprim | Amikacin, tobramycin, etc  Macrolides  Most cephalosporins  Chloramphenicol  Fluoroquinolones  Clindamycin  Co-amoxiclav  Other tetracyclines  Fidaxomicin  Piperacillin-tazobactam, etc  Temocillin  Vancomycin, teicoplanin | Aztreonam  Ceftobiprole,  Ceftaroline  Ceftazidime-avibactam  Ceftolozane-tazobactam  Colistin  Dalbavancin  Daptomycin  Carbapenems  Fosfomycin IV  Linezolid / tedizolid  Televancin  Tigecycline |

With regard to resistance inappropriate prescribing, including antibiotic related factors (spectrum of activity, cidality, mutation rates, dose, and duration (especially of “broad” spectrum antibiotics), lack of de-escalation cocktails) as well as completely unnecessary antibiotics all contribute to resistance. Also, up to 20% of hospitalized patients who receive antibiotics suffer an adverse effect, and each day of antibiotic use increases the risk of C. difficile infection, acute kidney injury, antibiotic resistance, and disruption of the gut microbiome (Rhee et al 2021).

Once an antibiotic is prescribed, regardless of whether the organism is susceptible, it is likely accurate bacterial identification is more difficult. Therefore, blind prescribing controlled without thought is likely to do more harm than good when considering both the patient and local resistance. Indeed, when 4h time related bundle strategies have been applied to community acquired pneumonia in the US, mortality remained the same but rates of *C.diff* went up.

The greatest increase in prescribing antibiotics is in the emergency department, presumably with NICE guidance, which requires adhering to 1h if sepsis is suspected. In hospital, overall antibiotics only increased by 3.5% per 1000 admissions, and the use of both IV antibiotics and broad-spectrum IV antibiotics in the emergency department doubled (PHE ESPAUR 2019).

Known antibiotic resistance to pathogens seen in sepsis is common. Of the common culprits of sepsis, the resistance patterns according to EARSS data collected between 2014 and 2019 are:

Gram Negative aetiology

Resistance to third generation cephalosporins in Klebsiella pneumoniae rose from 9.3% to 13.2% and to quinolones from 7.7% to 12.8%, but carbapenem resistance remained uncommon (0.8% to 0.7%). Pseudomonas aeruginosa became increasingly resistant to piperacillin tazobactam (4.0% to 5.6%) and quinolones (5.4% to 8.7%), but there was little change to ceftazidime (4.6% to 5.0%) or carbapenems (6.3% to 5.9%). In the same period, Escherichia coli resistance to third generation cephalosporins and quinolones changed little (10.5% to 11.5%, 16.8% to 17.8%) and carbapenem resistance was rare (0.1% to 0.0%).

Gram Positive aetiology

In contrast, resistance of Staphylococcus aureus to methicillin fell from 11.3% to 6.0% following a national MRSA reduction scheme.

**Breadth of patient diversity and treatment needs**

As the disease is difficult to define and treatments are varied, considerable skill is needed to ensure effective prescribing or with holding of antibiotics. A recent review has shown the outcome of timeliness varies considerably from clinical setting to setting (Asner, Desgranges et al. 2021). This is not surprising as research is very difficult due to the challenge of all-cause mortality being a notoriously challenging end point and heavily confounded by comorbidities and IDSA working group commented on need for better education of researchers (Rhee, Chiotos et al. 2021).

This makes writing guidance difficult and there have been many who have tried.

However, 1h treatment bundles from SSC have faced criticism for the same reason the 4h treatment bundles of pneumonia have in the US. The current AoMRC guidance in development aims to clarify a more evaluative approach. Education would seem more important than mobile apps and bundles, the former of which is often local and is likely to be of variable quality. When specialist teams are implemented especially in the Emergency Department are suggested to improve outcomes in terms of survival (Viale, Tedeschi et al. 2017). Sepsis teams, however, have operational implications that could be challenging.

**Topics need to be addressed**

The needs for guidance are:

1. How to prevent patients with infection progressing to sepsis in the community or hospital by better educational understanding and tools among patients, carers and HCPS
2. How to develop and use early warning tools such as NEWS2, SOFA etc.
3. How to better develop and use of tools for diagnosis of specific bacterial infection rather than is there likelihood of bacterial infection
4. How to give treatment for infection and bacterial sepsis balancing rapidly effective antibiotics minimising infection and understanding local resistance patterns
5. How to operationally manage emerging research and new guidance in sepsis, and support education of the emergency department, ward and ICU staff and call in additional help including sepsis teams.

# Sepsis training should be mandatory and delivered by doctors with relevant experience of current research and guidance.

## Current initiatives

Surviving sepsis Campaign has guidance documents and educational events and tools – predominantly aimed at critical care. AoMRC has a working party looking at using NEWS2 and timeliness of prescribing. NICE have guidance last updated in 2017. The sepsis trust has educational tools for health care professionals and patients. In the UK, the challenge of choosing an antibiotic is largely devolved to the microbiologist and not addressed in detail in most mobile apps.

## Specialists in antibiotic prescribing

With the decline of investment in new antibiotics due to the clinical pressure to reduce prescribing, there is less pressure to educate on use of antibiotics. Increasingly, hospitals use a phone app giving two choices for each type of infection and only when the patients reach level 2 (HDUs) or level 3 (ICUs) are microbiologists seen in a regular ward round.

The NHS web site states there are four distinct but very much interdependent infection specialties: Infectious Diseases (ID), Medical Microbiology (MM), Medical Virology (MV) and Tropical Medicine (TM). However, it also includes aspects of public health. However according to an ECCMID survey in 2008 Mike Mcendrick presented that UK has almost the fewest ID physicians per head of population in Europe. Infectious diseases physicians play an critical role in healthcare in most countries (Walensky, Del Rio et al. 2017). Whilst substituted by clinical microbiologists to some extent in the UK as infection is such a critical component of majority of deaths, the call for more infectious disease educational should be heeded. The same call surely applies to better sepsis prescribing.

This lack of clear structure of infectious disease physicians as Key Opinion Leaders in the UK is perhaps something that AoMRC could address. Whilst there are good microbiologists, pharmacists, intensivists and clinical pharmacologists, there are few ID physicians addressing best practice, especially in understanding antibiotic stewardship of which education is a major component.

# How FPM can help

## Currently we contribute to the sepsis collaborative group in AoMRC

This is a great multidisciplinary collaboration that has highlighted the challenges in early treatment with antibiotics potentially using NEWS2.

This collaboration could be extended to establish consensus on understanding antibiotics, research and prescribing. Resistance is a much bigger burden in ICU than in the community, and stewardship is really challenging. Many pathogens, such as *P. aeruginosa* and Acinetobacter, are intrinsically resistant to most antibiotics. FPM could field antibiotic specialists to this group.

## Sepsis is often downstream of non- septic infections training

**Understanding what depth of knowledge physicians have on ID**

FPM is considering scoping surveys or other forms of research into the types of education given to physicians on ID prescribing, the level of understanding these physicians have, and what and how FPM might support this understanding. See below under research.

**Innovation in treatments**

Pharmaceutical physicians are at the forefront of the development of new antibiotic interventions, which involves understanding of both drug characteristics and the potential harmful effect including both adverse effects to the patient and resistance propensity. This knowledge may be helpful in introducing new treatments which currently appear on the “Reserve List”. FPM members are involved in various AMR initiatives globally.

**Education in treatment of infections by different antibiotics**

It is not only essential for ED staff to call a microbiologist but also to be able to understand the aspects of diagnostics and antibiotics – as infection is omnipresent. Therefore, more specialists should be trained, and prescribing physicians or nurses should have enough knowledge of antibiotics to interpret prescribing instructions from mobile apps with greater expertise.

Members of FPM have a deep knowledge of both translational research and phase III placebo controlled and adaptive post licensing designs for treatment of bacterial infection by antibiotics. This includes understanding patterns of resistance from *in vitro* and *in vivo* studies as well as clinical outcomes and modelling. Pharmaceutical medicine is about generating information for doctors to use at individual patient level (tailored to the source infection and the antibiotic to be used) as well us understanding more global health technology assessment. In that context we can support and inform training in the treatment of infection. This could involve supporting materials and media, as well as formal modular training.

**Training for critical care sepsis teams**

FPM has pharmaceutical physicians who train their colleagues in pharmaceutical companies to support clinical training on prescribing . Companies may therefore be willing to help by contributing advice, materials and other IP, at arm’s length.

## Diagnostics

FPM has an expert policy group on medical devices and diagnostics. Some of the members of the group are specifically involved in developing diagnostics for bacterial identification, and could consider supporting the generation of more information on latest innovations and on the patient and operational barriers to implementation constraints. Diagnostics will be critical to improving antibiotic prescribing.

Currently, the time taken to return sensitivity on blood cultures in some hospitals means inappropriate prescribing is sometimes inevitable through no-one’s fault.

## Research

*Stewardship*

Managing the stewardship in hospitals is a major challenge since, in settings such as ICU, simply not prescribing is not an option. Also, such things as understanding of the impact of carabapenem resistance on other beta lactams is poorly understood. Pharmaceutical medicine has access to substantial clinical raw data and in vitro and in vivo data, which may be of help in terms of developing better understanding of resistance emergence to guide stewardship.

*Medical affairs research*

FPM is considering applying for research grants, from pharmaceutical companies and other sources, for performing research on how clinicians actually prescribe antibiotics. Whilst there is a huge amount of National and local level research around sepsis, we think it might be valuable to relate more to the antibiotic aspects of the patient infection journey that leads to sepsis and how we can help by making better information available for prescribing than is in the current SmPC and NICE guidance distilled into mobile apps.

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**Appendix**

Findings of UK National Confidential Enquiry into Patient Outcome and Death Just Say Sepsis survey

* 184/544 (33.8%) hospitals in this study had no formal sepsis protocol
* 309/343 (90.1%) hospitals with sepsis protocols had based them on published guidelines
* Most hospitals with protocols (305/321; 95%) stipulated that action should be taken within one hour of diagnosis of sepsis
* Of hospitals with protocols for recognition and management of sepsis, there was no formal education in the use of the protocol on general wards for medical staff in 65/305 (21.3%) and nursing staff in 86/314 (27.4%)
* In 518/532 (97.4%) hospitals, the hospital protocol policies and guidelines were immediately available on the hospital intranet
* The majority of hospitals without sepsis protocols (154/165; 93.3%) did have protocols for the identification of the deteriorating patient
* 95/186 (51.1%) acute hospitals stated that there was a system in place for receiving a pre-alert for patients arriving to the emergency department with sepsis
* The vast majority (530/538; 98.5%) of hospitals have track and trigger systems for monitoring sick patients and these were uniformly linked to escalation protocols (516/527; 97.9%)
* 199/223 (89.2%) hospitals with critical care facilities had a Critical Care Outreach Team or equivalent and 96/196 (49%) of these were available 24/7
* One in five hospitals (57/258; 22.1%) without critical care facilities did not have formal arrangements for the transfer of patients needing critical care
* 55/215 (25.6%) acute hospitals utilised specialised proformas to identify and monitor patients with sepsis
* 63/212 (29.7%) acute hospitals stated that there was no policy in place covering staff handovers. However,270/287 (94.1%) hospitals with a policy set aside time for the formal handover of patients between doctors’ shifts
* The vast majority of acute hospitals (224/226; 99%) had an antimicrobial policy and although 139/204 (68.1%) of acute hospitals had daily microbiology ward rounds on ICU (level 3), only 20/194 (10.3%) and 13/196 (6.6%) of acute hospitals reported having daily microbiology ward rounds on general medical or surgical wards (respectively).
* Only 29/519 (5.6%) hospitals in the study had leaflets to give to patients to provide information about sepsis
* Only 78/215 (36.3%) acute hospitals had any form of follow-up service for patients with sepsis
* Half of the hospitals in the study (166/322; 51.6%) had appointed a lead clinician for sepsis
* Less than half of acute hospitals (90/204; 44%) were carrying out audit of the timely treatment of severe sepsis
* 43/217 (20%) hospitals had a means of centrally recording incidents of severe sepsis