Antimicrobial Resistance Programme
Public Health Wales

The Microbiology of Severe Sepsis

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The document will be distributed to:
- The sub group for the surveillance of antimicrobial resistance and usage in Critical Care
- WICS
- RRAILS/ 1000 livesplus
- Critical Care Networks

Purpose of Document:
To provide information on resistance rates for bacteraemias by clinical syndrome (community and hospital) in the critical care setting in Wales, and guidance for the treatment of sepsis of unknown origin, including the start smart – then focus initiative from Department of Health.
INTRODUCTION

Definitions

- Severe sepsis is defined as the presence of one or more organ system dysfunction in the context of sepsis.
- Septic Shock is defined as patients who have evidence of hypoperfusion (high lactate) or a persistently low blood pressure after initial fluid resuscitation.

Sepsis claims over 37,000 lives in the United Kingdom annually - more than lung cancer and more than breast cancer and bowel cancer combined. Causative organisms may not always be identified in sepsis; however organisms cultured and identified from blood stream samples provides some guidance in the management of antibiotic therapy.

The top 10 bacteraemia rates are published by Public Health Wales annually (see Table 1). The majority of the top 10 organisms can be grouped into gram negative (GN) organisms (Escherichia coli, Enterobacter spp. Klebsiella spp. and Proteus spp. excluding Pseudomonas aeruginosa), and Staphylococcus aureus (MRSA and MSSA). Providing resistance rates will guide empiric treatment, until an organism can be identified and appropriate treatment based on local resistance patterns prescribed. Resistance rates are presented by clinical syndrome i.e. samples taken in the community including GP surgeries, A&E, MAU, CDU, and OP clinics are classed as ‘Community’; and samples taken in the hospital including all wards, units and theatres are classed as ‘Hospital’.

Table 1: Top ten blood stream infections for All Wales: 01/01/2012 to 31/12/2012

<table>
<thead>
<tr>
<th>Rank</th>
<th>Organism</th>
<th>Rate per 100,000 bed days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Escherichia coli</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>Staphylococcus aureus (MSSA)</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>Enterococcus species</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>Klebsiella species</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>Streptococcus pneumoniae</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>Coagulase-negative staphylococcus</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>Pseudomonas aeruginosa</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>Staphylococcus aureus (MRSA)</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>Proteus species</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>Enterobacter species</td>
<td>4</td>
</tr>
</tbody>
</table>

References

1. The College of Emergency Medicine: Clinical Standards for Emergency Departments (Feb 2013)
2. Sepsis Trust UK http://sepsistrust.org/sepsis/
5. Rapid response to Acute Illness (RAAI) www.1000livesplus.wales.nhs.uk
EVIDENCE: Resistance rates

Gram negative bacteraemias - COMMUNITY

Figure 1 shows the patterns of resistance for gram-negative bacteraemias (excluding Pseudomonas spp.) from blood cultures taken in the community across Wales (including GP surgeries, A&E, MAU, CDU, and OP clinics).

- Co-amoxiclav has been used by many centres for the empiric treatment of sepsis, but resistance in gram negative bacteraemia from community samples has increased from 22% to 36% in the last 8 years.
- Piperacillin/tazobactam plus gentamicin is recommended for the treatment of sepsis of unknown origin; in 2012 the co-resistance to piperacillin/tazobactam and gentamicin for community GN bacteraemias was 1.5%.
- For penicillin allergic patients please follow local antibiotic guidance.
- Carbapenem resistance remains extremely low in Wales, although coliforms that produce carbapenemases and are resistant to carbapenems and multiple other antibiotics have been identified. Carbapenem use must be restricted, where possible, in order to prevent spread of such organisms.

Figure 1: Resistance rates for Gram Negative bacteraemia from Community blood culture samples (2005 to 2012).

<table>
<thead>
<tr>
<th>Year</th>
<th>3GC</th>
<th>COA</th>
<th>CARB</th>
<th>CXM</th>
<th>FQ</th>
<th>GEN</th>
<th>PTZ</th>
<th>PTZ/GEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>6.2</td>
<td>22.9</td>
<td>0.4</td>
<td>10.1</td>
<td>12.7</td>
<td>4.6</td>
<td>6.7</td>
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<tr>
<td>2006</td>
<td>8.0</td>
<td>22.1</td>
<td>0.5</td>
<td>11.9</td>
<td>14.1</td>
<td>6.0</td>
<td>6.9</td>
<td>2.0</td>
</tr>
<tr>
<td>2007</td>
<td>8.4</td>
<td>27.4</td>
<td>1.9</td>
<td>14.0</td>
<td>14.4</td>
<td>6.3</td>
<td>6.1</td>
<td>0.8</td>
</tr>
<tr>
<td>2008</td>
<td>12.4</td>
<td>29.5</td>
<td>2.1</td>
<td>19.0</td>
<td>18.9</td>
<td>6.4</td>
<td>6.7</td>
<td>0.7</td>
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<tr>
<td>2009</td>
<td>11.7</td>
<td>33.5</td>
<td>2.2</td>
<td>18.0</td>
<td>18.5</td>
<td>6.7</td>
<td>7.3</td>
<td>1.2</td>
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<tr>
<td>2010</td>
<td>10.6</td>
<td>36.5</td>
<td>2.2</td>
<td>16.8</td>
<td>18.0</td>
<td>7.6</td>
<td>6.7</td>
<td>1.1</td>
</tr>
<tr>
<td>2011</td>
<td>11.2</td>
<td>33.0</td>
<td>1.8</td>
<td>17.4</td>
<td>17.0</td>
<td>7.2</td>
<td>6.1</td>
<td>1.4</td>
</tr>
<tr>
<td>2012</td>
<td>11.3</td>
<td>35.9</td>
<td>1.8</td>
<td>17.8</td>
<td>18.4</td>
<td>8.6</td>
<td>6.4</td>
<td>1.5</td>
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</table>

Key: 3GC = resistance to cefotaxime &/or ceftazidime, ceftriaxone and cefpodoxime; COA = co-amoxiclav; CARB = resistance to ertapenem &/or imipenem and meropenem; CXM = cefuroxime; FQ = ciprofloxacin &/or levofloxacin; GEN = gentamicin; PTZ = piperacillin/tazobactam; PTZ/GEN = co-resistance to piperacillin/tazobactam and gentamicin.
**Gram negative bacteraemias - HOSPITAL**

Figure 2 shows the patterns of resistance for gram-negative bacteraemias (excluding Pseudomonas spp.) from blood cultures taken in the hospital (including all wards, units and theatres).

- Resistance rates are significantly higher for samples taken in the hospital than in the community e.g. in 2012 the co-amoxiclav rate for GN bacteraemia from community samples was 35.9% compared with 46.8% resistance in the GN bacteraemia samples from the hospital setting.
- **Piperacillin/tazobactam plus gentamicin** is recommended for the treatment of sepsis of unknown origin for this clinical syndrome.
- For penicillin allergic patients please follow local antibiotic guidance.
- In 2012, co-resistance to piperacillin/tazobactam and gentamicin for hospital GN bacteraemias was 1.8%.

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**Figure 2: Resistance rates for Gram Negative bacteraemia from Hospital blood culture samples (2005 to 2012).**

Key: 3GC = resistance to cefotaxime &/or ceftazidime, ceftriaxone and cefpodoxime; COA = co-amoxiclav; CARB = resistance to ertapenem &/or imipenem and meropenem; CXM = cefuroxime; FQ = ciprofloxacin &/or levofloxacin; GEN = gentamicin; PTZ = piperacillin/tazobactam; PTZ/GEN = co-resistance to piperacillin/tazobactam and gentamicin.
**Staphylococcus aureus bacteraemias - COMMUNITY**

Figure 3 shows the patterns of resistance for *Staphylococcus aureus* bacteraemias from blood cultures taken in the Community (including GP surgeries, A&E, MAU, CDU, and OP clinics).

- Resistance to flucloxacillin decreased between 2008 and 2012, reflecting the decrease in the prevalence of MRSA bacteraemias.

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**Figure 3: Resistance rates for *Staphylococcus aureus* bacteraemia from Community blood culture samples (2005 to 2012).**

<table>
<thead>
<tr>
<th>Year</th>
<th>ERY</th>
<th>FLU</th>
<th>FUS</th>
<th>GEN</th>
<th>MUP</th>
<th>TET</th>
</tr>
</thead>
<tbody>
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<td>2005</td>
<td>29.2</td>
<td>26.6</td>
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<td>0.6</td>
<td>2.1</td>
<td>2.9</td>
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<td>2006</td>
<td>24.1</td>
<td>21.3</td>
<td>15.5</td>
<td>0.9</td>
<td>1.7</td>
<td>6.5</td>
</tr>
<tr>
<td>2007</td>
<td>26.8</td>
<td>28.2</td>
<td>9.7</td>
<td>1.0</td>
<td>2.6</td>
<td>5.3</td>
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<td>2008</td>
<td>28.1</td>
<td>29.9</td>
<td>10.7</td>
<td>5.4</td>
<td>1.4</td>
<td>3.4</td>
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<tr>
<td>2009</td>
<td>27.4</td>
<td>27.1</td>
<td>9.4</td>
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<td>2.6</td>
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<td>2011</td>
<td>21.5</td>
<td>19.5</td>
<td>13.1</td>
<td>0.8</td>
<td>3.6</td>
<td>5.8</td>
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<tr>
<td>2012</td>
<td>19.8</td>
<td>14.9</td>
<td>12.2</td>
<td>4.3</td>
<td>2.1</td>
<td>3.8</td>
</tr>
</tbody>
</table>

Key: ERY = erythromycin; FLU = flucloxacillin; FUS = fusidic acid; GEN = gentamicin; MUP = mupirocin; TET = tetracycline.
Staphylococcus aureus bacteraemias - HOSPITAL

Figure 4 shows the patterns of resistance for *Staphylococcus aureus* bacteraemias from blood cultures taken in the Hospital (including all wards, units and theatres).

- Resistance to flucloxacillin has decreased across time, reflecting the decrease in the prevalence of MRSA bacteraemias.
- Resistance to flucloxacillin is higher for samples taken in the hospital than in the community reflecting the higher prevalence of MRSA bacteraemia in the secondary care setting.
- Patients who are known or thought to have MRSA carriage should be treated according to local guidance.

![Figure 4: Resistance rates for *Staphylococcus aureus* bacteraemia from Hospital blood culture samples (2005 to 2012).](image)

**Key:** ERY = erythromycin; FLU = flucloxacillin; FUS = fusidic acid; GEN = gentamicin; MUP = mupirocin; TET = tetracycline.
NATIONAL RESISTANCE RATES - 2012

Table 2 shows the 2012 All-Wales resistance rates for GN bacteraemia and Staphylococcus aureus by clinical syndrome. Co-resistance to piperacillin/tazobactam and gentamicin in GN bacteraemias was less than 2%, showing this regimen should provide good coverage for these clinical indications.

Table 2: All-Wales resistance rates by organism group and clinical syndrome 2012

<table>
<thead>
<tr>
<th>Organism group</th>
<th>3GC</th>
<th>COA</th>
<th>CARB</th>
<th>CXM</th>
<th>FQ</th>
<th>GEN</th>
<th>PTZ</th>
<th>PTZ/GEN</th>
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</thead>
<tbody>
<tr>
<td>GN bacteraemia Community (n=1,289)</td>
<td>11.3</td>
<td>35.9</td>
<td>1.8</td>
<td>17.8</td>
<td>18.4</td>
<td>8.6</td>
<td>6.4</td>
<td>1.5</td>
</tr>
<tr>
<td>GN bacteraemia Hospital (n=1,507)</td>
<td>17.0</td>
<td>46.8</td>
<td>1.4</td>
<td>29.5</td>
<td>20.0</td>
<td>10.8</td>
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<td>1.8</td>
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</table>

<table>
<thead>
<tr>
<th>Organism group</th>
<th>ERY</th>
<th>FLU</th>
<th>FUS</th>
<th>GEN</th>
<th>MUP</th>
<th>TET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus Community (n=308)</td>
<td>19.8</td>
<td>14.9</td>
<td>12.2</td>
<td>4.3</td>
<td>2.1</td>
<td>3.8</td>
</tr>
<tr>
<td>Staphylococcus aureus Hospital (n=552)</td>
<td>24.3</td>
<td>22.6</td>
<td>13.8</td>
<td>4.0</td>
<td>3.4</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Key: 3GC = resistance to cefotaxime &/or ceftazidime, ceftriaxone and cefpodoxime; COA = co-amoxiclav; CARB = resistance to ertapenem &/or imipenem or meropenem; CXM = cefuroxime; FQ = ciprofloxacin &/or levofloxacin; GEN = gentamicin; PTZ = piperacillin/tazobactam; PTZ/GEN = co-resistance to piperacillin/tazobactam and gentamicin; ERY = erythromycin; FLU = flucloxacillin; FUS = fusidic acid; MUP = mupirocin; TET = tetracycline.

ANTIBIOTIC THERAPY: Sepsis of unknown origin

From the preceding data, it is clear that antimicrobial resistance is an issue for the empirical treatment of severe sepsis, where therapy with effective antimicrobial coverage of likely organisms is required within 1 hour. The combination of piperacillin/tazobactam plus gentamicin will cover 98% of Gram negative organisms, 95% of S. aureus (partial initial coverage for MRSA provided by gentamicin), 98% of Streptococcus pneumonia, and most Enterococcus spp. Sepsis caused by Pseudomonas spp. is predominantly seen in immunocompromised patients who should be treated according to local guidelines. However it is useful to note that co-resistance to piperacillin/tazobactam and gentamicin was not detected in Pseudomonas aeruginosa from blood cultures across Wales in 2012.

The following antibiotic regimen is recommended for the prompt and initial treatment of severe sepsis of unknown origin – in all other cases of sepsis, and for penicillin allergic patients please follow local antibiotic guidance:

- **Piperacillin/tazobactam** 4.5g IV TDS PLUS
- **Gentamicin** 6mg/kg administered IV

These recommendations on initial antibiotic therapy in severe sepsis of unknown origin are a result of a consensus of ICU Consultants, Clinical Microbiologists and Pharmacists in Wales. These recommendations are the current recommendations, and can/will change as the resistance data changes.

Review date for recommendations: September 2015
**SEPSIS SIX BUNDLE**

**Appropriate and timely treatment for severe sepsis within 1 hour of diagnosis**\(^5,6\)
- Oxygen - TARGET saturations >94%
- Blood Culture - PRIOR to IV antibiotics
- IV antibiotics – see recommendations above
- Fluid Resuscitation
- Serum Lactate and Hb - Ensure Hb >70g/L
- Hourly Urine Output Monitoring - Catheterisation or self-void.

**Resuscitation Bundle within 6 hours of diagnosis**\(^5,6\)
- Serum lactate measured
- Blood cultures obtained prior to antibiotic administration
- From the time of presentation, broad-spectrum antibiotics to be given within 3 hours for ED admissions and 1 hour for non-ED ICU admissions
- In the event of hypotension and/or lactate >4mmol/L (36mg/dL):
  - Deliver an initial minimum of 20 ml/kg of crystalloid (or colloid equivalent)
  - Give vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) > 65 mm Hg.
- In the event of persistent arterial hypotension despite volume resuscitation (septic shock) and/or initial lactate >4 mmol/L (36 mg/dl):
  - Achieve central venous pressure (CVP) of >8 mm Hg
  - Achieve central venous oxygen saturation (ScvO2) >70%

**SOURCE CONTROL**

Source control is the removal or drainage of infected tissue or collections. Source control and initial antimicrobial therapy requires the formulation of a differential diagnosis based on history, clinical examination and appropriate imaging. The management of severe sepsis and septic shock advocates removal of the source of infection by surgical intervention, radiological guided drainage and where the source is potentially an intravascular device its prompt removal. Where feasible control should be as soon as possible and evidence suggests within 12 hours following diagnosis.\(^7,8\)
ANTIMICROBIAL STEWARDSHIP
“Start Smart – then Focus”9

All Clinicians should ideally within one hour (or as soon as possible)

START SMART:
- Initiate prompt effective antibiotic treatment within one hour (or as soon as possible) in patients with life-threatening infections
- Document on drug chart and in medical notes: Route, Indication, Dose, Duration (RIDD)

Antibiotics in hospitals are often continued unnecessarily because clinicians caring for the patient do not have information indicating why the antibiotics were initially commenced and how long they were planned to be continued. This challenge is compounded where primary responsibility for patient care is frequently transferred from one clinician to another. Ensuring that all antibiotic prescriptions are always accompanied by an indication, the correct dose and a clear duration will help clinicians change or stop therapy when appropriate.

- Obtain Cultures First
Knowing the susceptibility of an infecting organism can lead to narrowing of broad spectrum therapy, changing therapy to effectively treat resistant pathogens and stopping antibiotics when cultures suggest an infection is unlikely.

THEN FOCUS

- Review the clinical diagnosis and the continuing need for antibiotics by 48 hours and make a clear plan of action - the “Antimicrobial Stewardship Decision”
Antibiotics are generally started before a patient's full clinical picture is known. By 48 hours, when additional information is available, including microbiology, radiographic and clinical information, it is important for clinicians to re-evaluate why the therapy was initiated in the first place and to gather evidence on whether there should be changes to the therapy.

- The five Antibiotic Stewardship Decision options are Stop, Switch, Change, Continue and OPAT:

  1. STOP antibiotics if there is no evidence of infection
  2. SWITCH antibiotics from intravenous to oral
  3. CHANGE antibiotics – ideally to a narrower spectrum, or broader if required
  4. CONTINUE and review again at 72 hours
  5. OUTPATIENT Parenteral Antibiotic Therapy (OPAT).

It is essential that the review and subsequent decision is clearly documented in the medical notes.