**Fifteen-Minute Consultation:  The Complexities of Empiric Antibiotic Selection for Serious Bacterial Infections – a Practical Approach.**

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**ABSTRACT**

Potentially life-threatening infections require immediate antibiotic therapy. Most early stage antibiotic treatment for these infections is empiric that is covering a range of possible target bacteria while awaiting culture results. Empiric antibiotic regimens need to reflect the epidemiology of most likely causative bacteria, type of infection and patient risk factors. Summary data from relevant isolates in similar patients helps to identify appropriate empiric regimens. At present, such data are mostly presented as hospital or other aggregate antibiograms, showing antimicrobial susceptibility testing results by bacterial species. However, a more suitable method is to calculate weighted incidence syndromic antibiograms (WISCAs) for different types of infections and regimens, allowing head-to-head comparisons of empiric regimens. Once there is confirmatory or negative microbiological evidence of infection, empiric regimens should be adapted to the identified bacterial species and susceptibilities or discontinued.

**THE CASE**

A 3 year-old boy with cerebral palsy is admitted to PICU with viral respiratory tract infection, intubated and invasively ventilated for 2 days because of respiratory failure. After extubation and in the absence of central venous catheters, he develops a fever without a clear focus. Clinically, the patient is stable from a respiratory point of view, but has signs of sepsis. He does not have any signs of meningitis. A urine sample is obtained without evidence of infection on dipstick. The child has not had any hospital admissions or antibiotic treatments in the last 15 months. The results from blood and urine cultures are pending.

**SHOULD THIS PATIENT BE TREATED WITH ANTIBIOTICS IMMEDIATELY?**

This largely depends on the clinical status of the patient and the confidence with which an immediate diagnosis can be made (Figure 1). In this scenario, the assessment of the patient as having sepsis would indicate that immediate empiric antibiotic treatment within one hour is required (1).

**What is empiric antibiotic treatment?**

This boy’s treatment will have to be empiric to cover potential bloodstream infection. Empiric antibiotic treatment has several “stages”, depending on how much information is available from microbiological cultures (Figure 2) (2). This in turn is influenced by the laboratory techniques in use and sample processing in specific laboratories.

Although systems for direct detection of bacterial nucleic acid in blood are available, these systems are very expensive, and have not been shown to be reliable or useful enough to either replace or supplement blood cultures in most settings. Moreover, even these techniques are not fast enough to give a result before antibiotic treatment is started. Many microbiology laboratories do now use new technologies, such as using matrix-assisted laser desorption/ionization time of flight (MALDI-TOF), to give same-day species identification of bacteria that have been isolated from blood cultures. This information can sometimes be useful in early review and de-escalation of on-going empiric therapy (3). However, antibiotic susceptibility testing will almost always have to be performed in the conventional manner, which requires a further overnight incubation. Thus there are at least two stages when empiric antibiotic therapy should be reviewed: when the blood culture signals positive and the identity of the isolate is established, and then on the following day when antibiotic susceptibilities become available. At each stage, microbiology staff can help with the interpretation of available data.

**IF SO, WHICH ANTIBIOTIC(S) SHOULD BE GIVEN?**

You may be working in a setting, in which hospital-level recommendations for empiric treatment are available. In such guidance, several options are often provided for children with sepsis, depending on age, the presence of comorbidities and the presence of central venous catheters. This demonstrates that there may be important information about the patient that needs to be considered before making a choice about empiric antibiotic treatment. At the hospital treating this patient, piperacillin/tazobactam would usually be used to empirically treat sepsis in children older than 1 month of age with underlying chronic comorbidities.

Your own hospital may not provide local guidance. In this case, the British National Formulary for Children (BNFC) suggests a number of possible regimens for treating community-acquired and hospital-acquired suspected bloodstream infections (Table 1) (4).

**Why is getting empiric antibiotic treatment right important?**

When selecting the optimal empiric regimen, the principal aim is to cover the expected spectrum of the causative bacteria according to age, patient characteristics and suspected site of infection. This will ensure that patients, in whom bacterial infection is eventually proven, are appropriately treated at an early stage of infection. Treatment concordance or discordance, meaning antibiotic therapy to which the isolate is susceptible or non-susceptible in vitro, is assessed in relation to microbiological results rather than describing a clinical response to treatment. For life-threatening infections, such as bloodstream infections, there is some evidence, mainly from adult patients, that early concordant antibiotic treatment improves patient outcomes (5).

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| **Infection** | **Antimicrobials** |
| Septicaemia in neonate <72 hours oldSepticaemia in neonate >72 hours old | Benzylpenicillin plus gentamicinIf Gram negative pathogen suspected: add cefotaxime, stop benzylpenicillin if Gram negative infection confirmedFlucloxacillin plus gentamicin OR amoxicillin plus cefotaximeSuggested duration 7 days |
| Septicaemia in child 1 month to 18 years, community-acquired | Amoxicillin plus aminoglycoside OR cefotaxime aloneIf Pseudomonas spp or resistant organisms suspected: use broad-spectrum antipseudomonal beta-lactam antibioticIf anaerobic infection suspected: add metronidazoleIf Gram positive infection suspected: add flucloxacillin OR vancomycinSuggested duration at least 5 days |
| Septicaemia in child 1 month to 18 years, hospital-acquired | Broad-spectrum antipseudomonal beta-lactam antibiotic, for example: piperacillin/tazobactam, imipenem/cilastin, meropenemIf Pseudomonas spp or multiresistant organisms suspected or if severe sepsis: add aminoglycosideIf MRSA suspected: add vancomycinIf anaerobic infection suspected: add metronidazole to a broad-spectrum cephalosporinSuggested duration at least 5 days |
| Septicaemia in presence of central vascular catheter | VancomycinIf Gram negative pathogens suspected: add broad-spectrum antipseudomonal beta-lactamConsider line removal |
| Meningococcal septicaemia | Benzylpenicillin or cefotaxime, if allergic give chloramphenicol |

Potentially to be used interchangeably: ampicillin and amoxicillin, ceftriaxone and cefotaxime, teicoplanin and vancomycin

Table 1: British National Formulary for Children 2015/2016 recommendations for empiric treatment of neonatal and paediatric septicaemia (4).

**SHOULD THIS PATIENT BE TREATED WITH A CARBAPENEM EMPIRICALLY?**

One option could be to simply administer the most “broad spectrum” antibiotic available to this child, for example, meropenem. Unfortunately, there are several problems with this type of approach:

1. Empiric antibiotic therapy is supposed to be given for a short period of time. However, in reality once a broad-spectrum antibiotic, such as a carbapenem, is commenced empirically it can be very difficult to de-escalate treatment promptly. From a clinical decision-making point of view, a positive blood or other culture would enable us to tailor this patient’s antibiotic therapy accordingly. However, his cultures may remain negative, while he may clinically still appear unwell. In this case, many clinicians would be worried about stopping or de-escalating empiric antibiotic treatment, a phenomenon that has been well described for neonatal intensive care patients, for example (6). In such a situation, broad-spectrum antibiotics are likely to be continued or even escalated in the absence of proof of infection. Prolonged empiric use of broad-spectrum antibiotics is known to be associated with a number of negative outcomes, such as a higher risk of necrotizing enterocolitis in neonates (7) and a higher risk of candida bloodstream infection in paediatric intensive care patients (8).
2. Using the most broad-spectrum options for all children also drives antimicrobial resistance locally and globally. The local impact of a policy of broad-spectrum antibiotic use was demonstrated in a trial carried out in neonatal intensive care in the Netherlands (9): An empiric regimen of amoxicillin and cefotaxime for the treatment of neonatal sepsis led to 18 times higher colonization with resistant Gram negative bacteria than when a more conservative regimen of penicillin plus tobramycin were used.
3. Our patient does not have any specific risk factors for bloodstream infection caused by multidrug resistant Gram-negative organisms. In patients with such risk factors (for example known colonization by extended-spectrum beta-lactamase producing bacteria) the treating physician may feel that a very broad regimen, such as meropenem, is a safe bet. Even the broadest antibiotic regimens, however, have gaps in their cover: *K. pneumoniae* bloodstream isolate resistance to carbapenems is known to be around 7% in children across Europe (10). This means that one would have to use ever more complicated combination regimens to ensure that all possible isolates, including carbapenem-resistant Enterobacteriaceae, are covered.

Thus, although we may feel that giving the broadest regimen will improve cover, this may not actually be the case, and this approach may be risky. Moreover, data are currently rarely available to support clinicians in daily practice that enable the cover of different regimens to be compared. However, clinicians could target empiric treatment better if this was available, and we address this issue in the next section.

**How are empiric antibiotic treatments selected?**

As mentioned above, patient-level knowledge of risk factors for a specific aetiology of sepsis is important in selecting empiric treatment. For example, if our patient had a central venous line, specific bacteria, such as *Staphylococcus aureus* or coagulase-negative staphylococci, would be more likely to be causing the bloodstream infection, and we would need to consider the cover provided by regimens for these pathogens. Similarly, knowledge of whether an infection is nosocomial and information on any recent antibiotic treatments is important.

Local antibiotic guidelines are usually based on aggregate microbiological data gathered at a local/hospital level for many patients, based on the assumption that isolates from these patients are representative of isolates likely to be encountered at this hospital. Such data are frequently summarized in the form of a hospital antibiogram (11). Table 2 is an example of a hospital antibiogram. These generally present resistance information by pathogen, summarizing the results of individual isolates for the key bacterial species over a specified period of time, for example, one year. Of note, not all data in a hospital antibiogram may be of clinical relevance. For example, while *Enterobacter* or *Serratia* spp may appear susceptible to cephalosporins *in vitro*, these agents should not be used to treat *Enterobacter* or *Serratia* spp. infection.

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| **Paediatric annual hospital antibiogram for 2015** |  | **Ampicillin** | **Amoxicillin/clavulanate** | **Cefotaxime** | **Ceftazidime** | **Cefuroxime** | **Ciprofloxacin** | **Clindamycin** | **Erythromycin** | **Flucloxacillin** | **Fusidic acid** | **Gentamicin** | **Imipenem** | **Linezolid** | **Penicillin** | **Piperacillin/tazobactam** | **Rifampicin** | **Teicoplanin** | **Tetracycline** | **Tigecycline** | **Trimethoprim** | **Vancomycin** |
|  | **N** |
| *E. coli*  | 22 | 65 | 16 | 11 | 8 | 18 | 22 |   |   |  |   | 11 | 0 |   |   | 3 |   |   |   | 0 |   |   |
| *Klebsiella* spp. | 8 |   | 13 | 9 | 7 | 16 | 9 |   |   |  |   | 5 | 0 |   |   | 9 |   |   |   | 3 |   |   |
| *Enterobacter* spp.  | 12 |   |   | 16 | 14 |   | 4 |   |   |  |   | 6 | 0 |   |   | 6 |   |   |   | 2 |   |   |
| *P. mirabilis*  | 4 | 34 | 6 | 2 | 1 | 1 | 8 |   |   |  |   | 7 |   |   |   | 1 |   |   |   |   |   |   |
| *Serratia* spp. | 8 |   |   | 10 | 0 |   | 5 |   |   |  |   | 0 | 0 |   |   | 7 |   |   |   | 2 |   |   |
| *P. aeruginosa*  | 9 |   |   |   |   |  | 6 |   |   |  |   | 3 | 4 |   |   | 5 |   |   |   |   |   |   |
| *S. aureus*  | 28 |   |   |   |   |   | 16 | 3 | 16 | 11 | 12 | 3 |   | 0 | 83 |   | 1 | 1 | 6 | 0 | 12 | 0 |
| Coag. neg. staphylococci  | 32 |   |   |   |   |   | 51 | 14 | 59 | 68 | 54 | 59 |   | 0 | 93 |   | 8 | 28 | 46 | 4 | 64 | 0 |
| *S. pneumoniae*  | 12 |   |   | 0 |   |   |  | 7 | 9 |  |   |   | 0 | 0 | 0 |   |   | 0 | 8 |   |   | 0 |
| *E. faecalis*  | 3 | 0 |   |   |   |   |   |   |   |  |   | 35 | 0 | 0 |   |   |   |   | 3 | 0 |   | 3 |
| *E. faecium* | 5 | 100 |   |   |   |   |   |   |   |  |   | 54 | 100 | 0 |   |   |   | 23 |   | 0 |   | 24 |

Table 2: Example of a hospital antibiogram. The number of isolates for 2015 is shown in the second column. Column headers are abbreviations for different antibiotics, for which susceptibilities may be tested. The numbers in the cells of the table represent the percentage of isolates found to be non-susceptible to the relevant antibiotic (these may be calculated by including isolates from the previous year as well, if sample size is low). Blank cells indicate that no relevant susceptibility testing results are available for this combination between bacterial species and antibiotic.

**WHAT TOOLS CAN SUPPORT EMPIRIC ANTIBIOTIC DECISIONS?**

While hospital antibiograms provide useful summaries of the resistance of pathogens to various antibiotics, they have several limitations in the context of empirical treatment decision-making: Although you may have a suspicion about the causative bacteria in a given patient, it is difficult to know for sure, and you would want to provide cover for less likely, but potentially dangerous candidates as well. It may be important to determine whether patients being treated for probable severe bacterial infection are colonized by multidrug resistant bacteria, for example, to provide appropriate empiric cover.

In our patient, there is a strong suspicion that the most likely type of infection is a primary bloodstream infection as he does not have any signs suggestive of urinary tract infection or meningitis and is stable from a respiratory point of view. We would therefore want to provide cover for bacteria that cause bloodstream infection in children seen at our centre.

One limitation is that many antibiograms will include isolates from all types of cultures, such as blood, urine and cerebrospinal fluid (11). While this approach increases the sample size of isolates, and therefore improves confidence in estimates of cover provided by different antibiotics, the pathogen and resistance patterns can differ between different sites of infection. In order to improve concordance of an empiric regimen for a specific site of infection, it is preferable to limit an antibiogram to isolates from relevant cultures: For suspected bloodstream infection, these would be blood cultures; for urinary tract infections, it would be urine cultures, and so on.

Another limitation is that antibiograms are rarely age-specific, even though pathogen and resistance patterns for children and adults are not the same (10, 12). Consequently, to support empiric antibiotic prescribing, clinicians require a summary statistic that will describe the likely overall cover of different antibiotic regimens given the type of patient and infection.

Finally, you would want to know whether the cover provided by different regimens is in fact similar. As with any other type of data, any observed differences may be down to chance and, depending on sample size, one’s confidence in the estimate of a regimen’s cover may be low, as in the case when the 95% confidence interval around the estimate is wide. Establishing the equivalence of regimens is important because guidelines such as “Surviving Sepsis” recommend selecting a regimen that provides cover for the whole likely spectrum of causative bacteria guided by local microbiological results (1).

**The weighted incidence syndromic combination antibiogram**

An alternative approach that overcomes the limitations of a hospital antibiogram is to present the microbiological data as a weighted incidence syndromic combination antibiogram (WISCA) (13-15). This describes the cover provided by different regimens, taking into account the distribution of pathogens and resistance patterns (weighted incidence) for a specific syndromic infection and can be calculated for both single and multiple (combination) antibiotic regimens. A further advantage is that it is possible to calculate 95% confidence intervals for the cover estimates, which allows clinicians to consider whether different regimens are likely to provide truly different cover (15). To select an appropriate regimen for our patient, we would want to review the WISCAs for candidate regimens, such as those listed in the BNFc, based on bloodstream isolates only.

Table 3 shows a WISCA that includes various regimens. These have been calculated from the data in Table 2 using a method based on a decision tree (15). You can see that amoxicillin plus gentamicin cover a similar proportion of isolates as piperacillin/tazobactam or meropenem, and may therefore be as good an option for empiric treatment in this instance. This assumes that all isolates in Table 2 were from blood cultures.

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| **Infection** | **Antimicrobial regimen** | **% of key isolates covered (95% confidence interval)** |
| Sepsis/bloodstream infection (based on blood culture isolates) | Amoxicillin plus gentamicin | 76% (69-82%) |
| Piperacillin/tazobactam | 73% (66-79%) |
| Ceftriaxone | 65% (58-72%) |
| Ceftriaxone or cefotaxime plus amoxicillin | 66% (59-73%) |
| Meropenem | 74% (68-81%) |

Table 3: Weighted incidence syndromic combination antibiograms (WISCAs) for specific empiric regimens when used for paediatric sepsis. The cover estimates are based on data in Table 2 and are presented with 95% confidence intervals.

The low level of cover provided by broad-spectrum antibiotics, such as piperacillin/tazobactam and meropenem, is mainly due to the inclusion of pathogens with high levels of resistance to these agents, for example coagulase-negative staphylococci (CoNS). It may not be necessary to provide early cover for CoNS, especially for children without central venous access lines who will not have sepsis due to CoNS.

As several regimens are very similar in empiric cover, the selection of a specific regimen can be carbapenem-sparing and consider additional factors: Piperacillin/tazobactam, for example, may have specific advantages in terms of renal toxicity compared with gentamicin in a combination treatment of amoxicillin and gentamicin and could be used to provide cover for specific bacteria of concern, such as *P. aeruginosa*. Our patient does not have risk factors for specific pathogens of concern, has normal renal function and could on the basis of the WISCAs in Table 3 perhaps have been empirically treated with amoxicillin plus gentamicin in the first instance.

**MOVING ON FROM EMPIRIC ANTIBIOTICS**

It is very important to adapt empiric antibiotic regimens once additional information becomes available. This is also the reason why it is critical to take all relevant microbiological samples before starting antibiotics, if at all possible. In the UK, changes to empiric antibiotics should follow the “Start Smart, Then Focus” approach (16).

In our patient, you may want to stop any antibiotic therapy if he is improving at 48 hours, urine and blood cultures are negative at this stage and clinically it appears that his deterioration was not due to infection. Equally, if his blood cultures grow a specific organism unlikely to be a contaminant, say *E. coli*, you may want to adjust therapy to the most narrow-spectrum option compatible with the specific microbiological susceptibilities of the isolate. If you are unsure about how to de-escalate treatment safely, your microbiology colleagues will be able to help you. At the same time, you should think about how long you might need to treat (see Table 1), and whether there will be an opportunity to switch from intravenous antibiotics to oral treatment. For example, if our patient had signs of urinary tract infection on dipstick, was improving clinically and his urine cultures grew *E. coli*, but his blood cultures remained negative, he may simply be suffering from a urinary tract infection and you could switch to oral treatment informed by the antibiogram of the urinary *E. coli* isolate.

**SUMMARY**

The selection of empiric antibiotic regimens for severe bacterial infections, when immediate treatment is required, needs to take into account the epidemiology of the targeted infection and key patient characteristics. This can be achieved by analysing available microbiological data, and presenting this in a clinically meaningful manner as a weighted incidence syndromic combination antibiogram (WISCA).

Figure 1

Bacterial infections for which empiric antibiotic treatment may be necessary.

Figure 2

Different stages of empiric antibiotic treatment, depending on available information from microbiological samples.

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