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Use of ceftazidime in children and options for treating pseudomonas infections

Summary

Ceftazidime, a third generation cephalosporin, has good in vitro activity against *P aeruginosa* and is clinically effective and safe in treating infections due to this organism. Cefepime, a fourth generation cephalosporin is equally effective in clinical trials. However, therapy with cefepime was associated with a significant increase in all cause mortality as compared to other broad spectrum beta lactams and carbapenems in a recent meta analyses. Extended spectrum penicillins like piperacillin and carbapenems are also effective in treating *P aeruginosa* infections and safe. Although for severe infections many clinicians prefer combination therapy with an antipseudomonal beta lactam and aminoglycoside, this combination is not shown to have additional benefits in clinical trials. On the other hand it is associated with increased nephrotoxicity and cost. Aminoglycosides, though active against *P aeruginosa*, are not usually used as monotherapy for this infection. Fluoroquinolones like ciprofloxacin can also be used when oral therapy is indicated.

There are no clinical trials which firmly establish superiority of one drug over another. Choice is generally based on local susceptibility patterns, nature of infection, cost and the potential to cause super infections and induce resistance. AMR is increasing to most antipseudomonal drugs and is worst for fluoroquinolones.

For parenteral therapy, ceftazidime, piperacillin and imipenem/meropenem are most often used and are at least equally effective and safe. Ceftazidime is primarily for infections proved or strongly suspected to be caused by *P aeruginosa* or other related bacteria like *Burkholderia cepacia* and *B pseudomallei*. It is the least expensive among the commonly used antipseudomonal antibiotics and there are no age restrictions for ceftazidime sodium.

Piperacillin-tazobactam is probably a better choice for polymicrobial infections like intra abdominal infections and for empirical therapy of serious infections where bacteria like ESBL producing *E coli* could also be possible pathogens. Super

infections are less with this drug as compared to cephalosporins. However, it is recommended only for those above 2 m and is expensive. BNF C states that it is not licensed for those under 12 yrs, except for neutropenia and complicated appendicitis, but provides dosage for neonates as well.

Aztreonam has action only against aerobic Gram negative bacteria and so is not useful for empiric therapy where Gram positives can also be involved. Imipenem is better reserved as second line drug. Colistin has been used parenterally, but only when there were no other options.

Cefipime is also used widely, but FDA has recently issued an alert on its safety.

Recommendation

Retain ceftazidime

Consider adding piperacillin/tazobactam in the complementary list since it is better for polymicrobial infections involving ESBL producers (eg intra-abdominal infections) as compared to ceftazidime, AMR rates may be lower, potential to induce resistance is lower, super infection rate is low

Infections caused by *P aeruginosa*

Pseudomonas aeruginosa is an important cause of serious infections in infants and children. These include nosocomial infections like bacteraemia, eye infections including endophthalmitis, CNS infections, ventilator associated pneumonia (VAP), skin and soft tissue infections following burns and trauma and UTI. It also causes a significant proportion of chronic suppurative otitis media (CSOM) and respiratory infections associated with cystic fibrosis. Infections in neutropenic and immunocompromised children can be due to *P aeruginosa*.

Nosocomial out breaks are reported from nurseries and pediatric ICUs [1-3]. *P aeruginosa* infection in children and neonates is associated with higher mortality[3-5]. Nosocomial infections are more common in developing countries where infection control practices are not fully satisfactory. In a review of data from developing countries, rates of neonatal infections among hospital-born babies were 3-20 times higher than those reported from industrialised countries [6]. *P aeruginosa* was an important pathogen.

Antibiotics with activity against *P aeruginosa*

P aeruginosa is resistant to most first line antibiotics. Antibiotics with activity against these bacteria

Antipseudomonal penicillins like ticarcillin and piperacillin (with or without beta lactamase inhibitors)

Third and fourth generation cephalosporins like Ceftazidime and cefepime,
Aminoglycosides

Aztreonam

Carbapenems like imipenem and meropenem

Fluoroquinolones like ciprofloxacin and levofloxacin

Colistin, polymixin B

There is insufficient data from clinical trials to establish superiority of any one. Policies on antibiotic choices differ in different areas and institutions. Therapy for infections proven or suspected to be caused by *P aeruginosa*, is decided based on susceptibility patterns of isolates from individual patients or current local AMR data and individual preferences. Nature and severity of infection, cost of therapy, potential to induce resistance and super infection rates are other considerations.

In general, most clinicians prefer two drugs together [7, 8] – ticarcillin/piperacillin+ aminoglycosides or ceftazidime/cefipime + aminoglycosides or ciprofloxacin+ aminoglycosides for severe infections. However there is insufficient data to support the efficacy of combination therapy as against monotherapy with third or fourth generation cephalosporins, anti pseudomonadal penicillins or imipenem/meropenem. Addition of aminoglycosides can increase nephrotoxicity and cost

AMR

AMR has appeared to all drugs and is increasing. Proportions of isolates resistant to each antibiotic vary from place to place. 94% and 93% respectively of *P aeruginosa* isolated from children during 1998-2004 from 52 sentinel hospitals in North America were susceptible to imipenem, and piperacillin-tazobactam. Only 1.4% and 2.3%, respectively were resistant to imipenem and cefepime [9]. In a study from Slovak republic, 1.2% of 169 *P. aeruginosa* were resistant to meropenem, 4.1% to piperacillin/tazobactam, 7.7% to ceftazidime and cefepime, 12% to amikacin and > 30% to ciprofloxacin [10]. Much higher rates are also reported from other areas in the

world. For example, in one study 60.9% of *P. aeruginosa* isolated from patients with burns were resistant to piperacillin, 53.4% to ceftazidime, 37.6% to imipenem, 59.3% to tobramycin, 80% to gentamicin, 62.4% to amikacin and 53.4% to ciprofloxacin [11].

Metallo-beta-lactamase (MBL)-producing *P. aeruginosa* isolates are resistant to almost all broad-spectrum beta-lactams and carbapenems and are increasingly being reported from several parts of the world from hospitals including neonatal facilities [12, 13] and in cystic fibrosis [14]

AMR can develop as a result of antibiotic therapy. Gentamicin, tobramycin, ciprofloxacin, ceftazidime, and imipenem have higher potential for inducing resistance as compared to amikacin, piperacillin, cefoperazone, cefepime and meropenem [15].

Evidence for efficacy and safety

Clinical trials evaluating antibiotics for proven serious *P. aeruginosa* infections especially in children are almost non-existent.

Empirical therapy to cover *P. aeruginosa* and also other potential pathogens is used in children with febrile neutropenia, cystic fibrosis and sepsis. Most reported trials are in these conditions.

Most reported clinical trials in adults and children show therapies under comparison to be equal in efficacy and safety. A recent meta-analysis comparing cefepime with other broad spectrum beta lactam antibiotics included 57 RCTs. All-cause mortality was higher with cefepime than other beta-lactams (RR 1.26; 95% CI 1.08-1.49).

Higher RRs were obtained for trials reporting adequate allocation-sequence generation (1.52; 1.20-1.92) and allocation concealment (1.36; 1.09-1.70). Baseline risk factors for mortality were similar. All antibiotics compared (ceftazidime, piperacillin-tazobactam, cefotaxime/ceftriaxone, imipenem/meropenem) had lower all cause mortality and the advantage was significant with piperacillin-tazobactam (RR 2.14; 1.17-3.89). With Cefepime, all cause mortality was higher in all types of infections (febrile neutropenia, pneumonia and other infections) and was significant for febrile neutropenia (RR 1.42; 1.09-1.84) [16]. The authors advise re-evaluation of policies where this drug is recommended. Based on this report FDA has issued an alert and states that it is reviewing safety issues related to cefepime

No significant differences between groups in over all treatment failure, superinfection, or adverse events were found. There was no significant difference in clinical failures between cefepime and ceftazidime, carbapenems or cefotaxime/ceftriaxone. However, clinical failures were significantly more in cefepime as compared to piperacillin-tazobactam (RR 1.09; 1.01-1.18). 0-40% of infections were due to *Pseudomonas* spp. [16]. Sub group analyses is not available

A systematic review found that the antibiotic most frequently related to superinfection was ciprofloxacin (38.1%), followed by cefotaxime (23.3%), imipenem (12%), meropenem (10.2%), cefepime (6.1%) and piperacillin-tazobactam (5.4%) [17].

Proven infections with *P aeruginosa*

A Cochrane review to determine the benefits of early antibiotic treatment in children and adults with cystic fibrosis to eradicate *P. aeruginosa*, identified three eligible studies and concluded that therapy brings about microbial eradication in the short term, but clinical benefits were unclear [18]. Another Cochrane review to determine benefits or harm of oral anti-pseudomonal antibiotic therapy in people with cystic fibrosis, colonised with *P aeruginosa* concluded that there is no evidence to suggest that oral therapy is better or worse than parenteral therapy based on four trials examining exacerbations (197 participants) and two trials examining long-term therapy (85 participants) [19]. Studies included in this trial are summarised in table 1. In a prospective, open, randomized trial comparing ceftazidime and aztreonam in children with CSOM without cholesteatoma and a pure culture of *P aeruginosa* growing in middle ear discharge, success rate defined as complete disappearance of discharge, was 84.6% in the ceftazidime group and 67% in the aztreonam group. There were 15 children in each arm (mean age 56 m and 48 m respectively). Two patients in each group had recurrence within 90 d from discontinuation of therapy [20]. In another study, ceftazidime was found to be useful for out patient treatment of CSOM caused by *P aeruginosa* [21]

During a period of 11 yrs, 14 children with burns and pan resistant *P aeruginosa* infection received parenteral colistin. Favourable response rate was seen in 78.8%. Overall mortality was 14 % and this was attributed to sepsis [22].

Cystic fibrosis

P aeruginosa can be isolated from a good proportion of patients including children with cystic fibrosis [23, 24] and antipseudomonal antibiotics are used frequently to treat an exacerbation. Extended-spectrum penicillins, cephalosporins, fluoroquinolones, aminoglycosides, meropenem, colistin are used for therapy [23, 24]. There is no clinical evidence for superiority.

B cepacia another cause of infections in cystic fibrosis [25] is most susceptible to ceftazidime [23, 26] and so is preferred in areas where this infection is also common. A Cochrane review of RCT comparing a single intravenous antibiotic with a combination of that antibiotic plus a second antibiotic in people with Cystic fibrosis included 8 trials. Six of these were done prior to 1988. Methodological quality was poor and results inconclusive [27].

A recent study showed that desired antibiotic concentrations were not reached in the sera and lungs of most patients with cystic fibrosis on ceftazidime and tobramycin [28]. Lower respiratory tract infections are listed as one of the indications for piperacillin/tazobactam therapy in BNF C. Ceftazidime is recommended for lung infections in cystic fibrosis in BNF C.

Sepsis

Approximately 8 -15% of blood stream infections in children can be due to *P aeruginosa* [29, 30]. *E coli* is another major pathogen. Antibiotic combinations used for therapy include cover for *P aeruginosa*.

A Cochrane review to evaluate beta lactam monotherapy with beta lactam+ aminoglycoside combination found that the latter carried a significant risk of nephrotoxicity RR 0.30 (95% CI 0.23-0.39). Other adverse events, clinical failure and all-cause fatality rates were unchanged [31]. 64 trials, randomizing 7586 patients, mostly adults with different types of serious infections and aetiologies, were included. No significant disparities emerged from subgroup analyses, including the assessment of patients with *P aeruginosa* infections. No differences in the rate of resistance development were observed.

Change in protocol for neonatal sepsis from ceftazidime + amikacin to piperacillin tazobactam resulted in significant reduction in MDR nosocomial infections in neonates in one unit [7]. The latter is currently one of the preferred options for neonatal nosocomial sepsis [29]. Sepsis is listed as one of the indications for

piperacillin/tazobactam therapy in BNF C. Ceftazidime is recommended for susceptible Gram positive and negative infections.

Febrile neutropenia

Gram negative bacilli like *E coli* and *P aeruginosa* are frequent pathogens [32]. Guidelines for antibiotic choices are usually made locally [33] because of differences in distribution of infecting organisms and varying AMR rates.

In a prospective randomized study, 50 children with febrile neutropenia were given cefepime or ceftazidime + amikacin as empirical therapy. Duration of fever, hospitalization, and antibiotic administration were longer in the ceftazidime + amikacin arm. The costs of the antimicrobial drugs, hospitalization, and total cost were lower in the cefepime arm [34]. In another randomised controlled trial in 76 episodes of febrile neutropenia in children, ceftazidime + amikacin (57%) and meropenem (72%) monotherapy had success rates which were not different statistically. Only 2 of the 27 patients with causative organism identified had *P aeruginosa* infection. Adverse effects were similar [35]. Cefepime + netilmicin, ceftazidime + amikacin and meropenem monotherapy were compared in febrile neutropenic children with malignancy in Turkey. Success rates were similar, but meropenem was more expensive than the two combinations evaluated [36]

Comparison of cefipime with ceftazidime monotherapy in 96 evaluable episodes in children found that the overall success rates were similar (69% vs. 71% respectively). The bacterial eradication rate was 33% with cefepime and 20% with ceftazidime and the rates of new infections were 10.4% and 4.2% respectively. Both drugs were well tolerated [37]. Similar results were observed in other trials also [38]

Early and complete responses were observed with ceftazidime-aminoglycosides in 108 (50.0%) and 133 (61.6%) of 216 episodes of febrile neutropenia in children with cancer in a retrospective analyses. Primary bacteremia and emerging bacteremia during treatment were 20 (9.3%) and 5 (2.3%) [39].

In a prospective non randomised trial using piperacillin-tazobactam+ amikacin in children with neutropenia, 77 (49.7 percent) episodes responded without a need for treatment modification [40]. Another multicentric retrospective survey also shows similar results [41]

Eighteen trials were included in a Cochrane review comparing oral with parenteral therapy in those with low risk of mortality. The mortality rates and treatment failure rates were similar. Quinolones alone or combined with other antibiotics had comparable results. Adverse reactions, mostly gastrointestinal were more common with oral antibiotics [42].

This is listed as one of the indications for piperacillin/tazobactam therapy in BNF C. Ceftazidime is recommended for susceptible infections due to Gram positive and negative bacteria.

Nosocomial pneumonia

P aeruginosa and other Gram negative bacilli are frequent causes of nosocomial pneumonias in children.

Thirty children aged <1 year with VAP occurring 5 or more days after intubation were randomized to receive cefepime or ceftazidime. Cure rates were similar and there were no major adverse events [43]. Efficacy and safety of Piperacillin-tazobactam is similar to that of ceftazidime [44] and imipenem ciliastatin [45].

Piperacillin-tazobactam or carbapenem are better choices in areas where ESBL producing bacteria are endemic [46]

Additional cover for Gram positive bacteria and fungi may be required for therapy of serious infections.

Intra-abdominal infections

Safety and efficacy of parenteral piperacillin/tazobactam were evaluated in 60 children with secondary peritonitis (90% following perforated appendicitis) in a multicenter study. 36 had poly microbial infections; *E coli* (52 isolates), *P aeruginosa* (16 isolates) and *Bacteroides* sp. (19 isolates). Clinical failure occurred in 4/ 43 evaluable patients. There were 2 clinically adverse events considered related to the study drug and several possibly related, mild and transitory, abnormalities in eosinophil counts and liver function tests [47].

Cefepime has activity similar to that of imipenem-ciliastatin for intra abdominal infections (Maxipime Label – Bristol-Myers Squibb)

Intra-abdominal infections and complicated appendicitis are listed as indications for piperacillin/tazobactam therapy in BNF C

Other infections where ceftazidime is recommended

Therapeutic concentrations of ceftazidime are reached in CSF and so is recommended for meningitis caused by *P aeruginosa* [48]. It is also recommended for catheter infections in children with HIV [49].

Related organisms like *B cepacia* can infect children with cystic fibrosis and ceftazidime is recommended in BNF C. In endemic areas melioidosis caused by *B pseudomallei* can occur in children also and is associated with high mortality rates [50, 51]. Ceftazidime is recommended for the initial parenteral therapy [51, 52]

Other issues

Ceftazidime

For children less than 12 yrs, L arginine containing formulations of ceftazidime are not recommended but sodium formulations can be used (label Fortaz, Ceptaz, Glaxo Smith Kline). Ceftazidime can be administered as continuous infusion. Here again there is no data to prove superiority [24].

Indications included in the label include different infections with *P aeruginosa* and also infections caused by other bacteria.

Since ceftazidime is excreted almost exclusively through kidneys, dosage has to be adjusted in those with renal impairment. When administered together with aminoglycosides, nephrotoxicity and ototoxicity increases. Concomitant use of chloramphenicol is also to be avoided.

With both ceftazidime and cefepime, serious and fatal encephalopathy, seizures, coma and myoclonus can occur especially in those with renal impairment. Other adverse events common to cephalosporins like hypersensitivity, super infections etc can also occur with both. Prothrombin activity can decrease.

Inducible type 1 beta lactamase mediated AMR can occur in *P aeruginosa*. Hence periodic susceptibility testing is recommended while using ceftazidime.

False positive urine glucose test, hyperbilirubinemia and jaundice are also reported

Cefepime

All cause mortality is higher with cefepime as compared to other broad spectrum beta lactam antibiotics and carbapenems [16]. Based on susceptibility data [9] and clinical efficacy [16] it is comparable to other antipseudomonal antibiotics.

Safety is established only above 2 m (Maxipime label Bristol Myers Squibb). Indications listed in the label include infections due to *P aeruginosa* (nosocomial pneumonia, febrile neutropenia, intra abdominal infections) and also other Gram negative bacilli and Gram positive cocci.

Piperacillin-tazobactam

P aeruginosa is susceptible to piperacillin alone. However, the combination is most widely available and used since it covers both piperacillin susceptible infections and those due to bacteria like *E coli* with beta lactamase (inhibited by tazobactam) mediated resistance to piperacillin. It is also useful for mixed infections caused by piperacillin susceptible and piperacillin resistant but combination susceptible bacteria. Indications in the label include infections where *P aeruginosa* could be one of the potential pathogens (eg nosocomial pneumonia) and also other infections due to susceptible bacteria like complicated appendicitis and peritonitis and other infections. Clearance is slower in children up to 9m and after that it is similar to adults (Zosyn label, Wyeth Pharmaceuticals). Dosage has to be adjusted in renal disease.

There is insufficient data to establish safety below 2 months.

BNF C states that it is not licensed for use in children under 12 yrs except for neutropenia and complicated appendicitis. However, BNFC has dosages for neonates.

If mixed *in vitro* with aminoglycosides, the latter can be inactivated

In a nosocomial pneumonia trial, > 90% developed adverse events both with piperacillin-tazobactam and imipenem. 11% discontinued therapy in the former group compared to 6.5% in the latter. Most events were GI and skin related. In children with intra abdominal infections, 27% developed adverse reactions and 2% discontinued (Zosyn label, Wyeth Pharmaceuticals). Fever [53] and serum sickness like syndrome[54] are also reported.

Antibiotic associated diarrhoea, super infections and clotting abnormalities can occur. It can interact with certain other drugs like probenecid, heparin, methotrexate etc (Zosyn label, Wyeth Pharmaceuticals).

Cost and dosage

International Drug Price Indicator Guide - buyer prices

| | DDD | Unit | Dosage | Cost US\$ | EML C listing |
|------------------------------|------|-------------------|---|--------------------|---------------------------|
| Ceftazidime* | 4 gm | 1gm | < 4 wks - 30mg/kg Q12H 1m-12 yr - 30-50 mg/kg Q8H | 2.4350 | 250 mg |
| Cefepime | 2gm | 1 gm | 2m-16yrs- 50mg/kg Q8- 12H | 6.7500 | |
| Piperacillin + tazobactam | 14gm | 4gm** + 0.5 | 2-9m- 80mg +10 mg/kg Q8H > 9m-100mg+ 12.5 mg/kg Q8H | 24.4596 | |
| Imipenem + ciliastatin | 2gm | 500 mg+ 500 mg | | 9.84 | 250+250 mg 500 +500 mg |
| Meropenem | 2 gm | 1 gm 500 mg | | 25.3456 16.7645 | |

*Ceftazidime

Only 1gm powder is available from IDPIG, Fortaz 500 mg available

Pentahydrate sodium may need to be specified

** shown as 4 mg in IDPIG

Ticarcillin, colistin, polymixin and aztreonam not listed

A study using Monte Carlo simulation suggests that the dosages of antipseudomonal drugs used are unlikely to result in bactericidal concentrations in children [55].

References

1. Orrett, F.A., *Fatal multi-resistant Pseudomonas aeruginosa septicemia outbreak in a neonatal intensive care unit in Trinidad*. Ethiop Med J, 2000. **38**(2): p. 85-91.
2. Brito, D.V., et al., *An outbreak of conjunctivitis caused by multiresistant Pseudomonas aeruginosa in a Brazilian newborn intensive care unit*. Braz J Infect Dis, 2003. **7**(4): p. 234-5.
3. Gerardin, P., et al., *[Pseudomonas aeruginosa infections in a neonatal care unit at Reunion Island]*. Arch Pediatr, 2006. **13**(12): p. 1500-6.
4. Ondrusova, A., et al., *Pseudomonas aeruginosa causing nosocomial meningitis in neonates and children: overview of 15 cases within 10 years*. Neuro Endocrinol Lett, 2007. **28 Suppl 2**: p. 20-1.

5. Gordon, A. and D. Isaacs, *Late onset neonatal Gram-negative bacillary infection in Australia and New Zealand: 1992-2002*. *Pediatr Infect Dis J*, 2006. **25**(1): p. 25-9.
6. Zaidi, A.K., et al., *Hospital-acquired neonatal infections in developing countries*. *Lancet*, 2005. **365**(9465): p. 1175-88.
7. Flidel-Rimon, O., et al., *Reduction in multiresistant nosocomial infections in neonates following substitution of ceftazidime with piperacillin/tazobactam in empiric antibiotic therapy*. *Acta Paediatr*, 2003. **92**(10): p. 1205-7.
8. *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th Edition*, ed. L.L. Brunton, et al. 2006.
9. Jones, R.N., et al., *Comparisons of parenteral broad-spectrum cephalosporins tested against bacterial isolates from pediatric patients: report from the SENTRY Antimicrobial Surveillance Program (1998-2004)*. *Diagn Microbiol Infect Dis*, 2007. **57**(1): p. 109-16.
10. Koprnova, J., et al., *Bacteremia due to Pseudomonas aeruginosa: results from a 3-year national study in the Slovak Republic*. *J Chemother*, 2005. **17**(5): p. 470-6.
11. Lamia, T., et al., *[Epidemiological profile and antibiotic susceptibility of Pseudomonas aeruginosa isolates within the burned patient hospitalized in the intensive care burn unit]*. *Tunis Med*, 2007. **85**(2): p. 124-7.
12. Fujimura, S., et al., *Relationship between the usage of carbapenem antibiotics and the incidence of imipenem-resistant Pseudomonas aeruginosa*. *J Infect Chemother*, 2007. **13**(3): p. 147-50.
13. Achour, W., et al., *[Nosocomial respiratory infection due to an imipenem-resistant Pseudomonas aeruginosa O: 12 strain in a Tunis's neonatal intensive care unit]*. *Pathol Biol (Paris)*, 2006. **54**(10): p. 596-9.
14. Valenza, G., et al., *Prevalence and antimicrobial susceptibility of microorganisms isolated from sputa of patients with cystic fibrosis*. *J Cyst Fibros*, 2008. **7**(2): p. 123-7.
15. Cunha, B.A., *Pseudomonas aeruginosa: resistance and therapy*. *Semin Respir Infect*, 2002. **17**(3): p. 231-9.
16. Yahav, D., et al., *Efficacy and safety of cefepime: a systematic review and meta-analysis*. *Lancet Infect Dis*, 2007. **7**(5): p. 338-48.
17. Alvarez, C., et al., *[Risk of superinfection related to antibiotic use. Are all antibiotics the same?]*. *Rev Esp Quimioter*, 2005. **18**(1): p. 39-44.
18. Wood, D.M. and A.R. Smyth, *Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis*. *Cochrane Database Syst Rev*, 2006(1): p. CD004197.
19. Remington, T., N. Jahnke, and C. Harkensee, *Oral anti-pseudomonal antibiotics for cystic fibrosis*. *Cochrane Database Syst Rev*, 2007(3): p. CD005405.
20. Somekh, E. and Z. Cordova, *Ceftazidime versus aztreonam in the treatment of pseudomonal chronic suppurative otitis media in children*. *Scand J Infect Dis*, 2000. **32**(2): p. 197-9.
21. Esposito, S., et al., *Ceftazidime for outpatient parenteral antibiotic therapy (OPAT) of chronic suppurative otitis media due to Pseudomonas aeruginosa*. *J Chemother*, 2000. **12**(1): p. 88-93.
22. Goverman, J., et al., *Intravenous colistin for the treatment of multi-drug resistant, gram-negative infection in the pediatric burn population*. *J Burn Care Res*, 2007. **28**(3): p. 421-6.

23. Banerjee, D. and D. Stableforth, *The treatment of respiratory pseudomonas infection in cystic fibrosis: what drug and which way?* *Drugs*, 2000. **60**(5): p. 1053-64.
24. Smyth, A. and J.S. Elborn, *Exacerbations in cystic fibrosis: 3--Management*. *Thorax*, 2008. **63**(2): p. 180-4.
25. Lambiase, A., et al., *Microbiology of airway disease in a cohort of patients with cystic fibrosis*. *BMC Infect Dis*, 2006. **6**: p. 4.
26. Zhou, J., et al., *Antimicrobial susceptibility and synergy studies of Burkholderia cepacia complex isolated from patients with cystic fibrosis*. *Antimicrob Agents Chemother*, 2007. **51**(3): p. 1085-8.
27. Elphick, H.E. and A. Tan, *Single versus combination intravenous antibiotic therapy for people with cystic fibrosis*. *Cochrane Database Syst Rev*, 2005(2): p. CD002007.
28. Moriarty, T.F., et al., *Sputum antibiotic concentrations: implications for treatment of cystic fibrosis lung infection*. *Pediatr Pulmonol*, 2007. **42**(11): p. 1008-17.
29. Yalaz, M., et al., *Neonatal nosocomial sepsis in a level-III NICU: evaluation of the causative agents and antimicrobial susceptibilities*. *Turk J Pediatr*, 2006. **48**(1): p. 13-8.
30. Orrett, F.A. and E. Changoor, *Bacteremia in children at a regional hospital in Trinidad*. *Int J Infect Dis*, 2007. **11**(2): p. 145-51.
31. Paul, M., et al., *Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis*. *Cochrane Database Syst Rev*, 2006(1): p. CD003344.
32. Paul, M., et al., *The epidemiology of bacteremia with febrile neutropenia: experience from a single center, 1988-2004*. *Isr Med Assoc J*, 2007. **9**(6): p. 424-9.
33. Mendes, A.V., R. Sapolnik, and N. Mendonca, *New guidelines for the clinical management of febrile neutropenia and sepsis in pediatric oncology patients*. *J Pediatr (Rio J)*, 2007. **83**(2 Suppl): p. S54-63.
34. Corapcioglu, F. and N. Sarper, *Cefepime versus ceftazidime + amikacin as empirical therapy for febrile neutropenia in children with cancer: a prospective randomized trial of the treatment efficacy and cost*. *Pediatr Hematol Oncol*, 2005. **22**(1): p. 59-70.
35. Hung, K.C., et al., *Monotherapy with meropenem versus combination therapy with ceftazidime plus amikacin as empirical therapy for neutropenic fever in children with malignancy*. *J Microbiol Immunol Infect*, 2003. **36**(4): p. 254-9.
36. Agaoglu, L., et al., *Cost-effectiveness of cefepime + netilmicin or ceftazidime + amikacin or meropenem monotherapy in febrile neutropenic children with malignancy in Turkey*. *J Chemother*, 2001. **13**(3): p. 281-7.
37. Chuang, Y.Y., et al., *Cefepime versus ceftazidime as empiric monotherapy for fever and neutropenia in children with cancer*. *Pediatr Infect Dis J*, 2002. **21**(3): p. 203-9.
38. Kebudi, R., et al., *Randomized comparison of cefepime versus ceftazidime monotherapy for fever and neutropenia in children with solid tumors*. *Med Pediatr Oncol*, 2001. **36**(4): p. 434-41.
39. Laoprasopwattana, K., et al., *Clinical outcome of febrile neutropenia in children with cancer using ceftazidime and aminoglycosides*. *Pediatr Hematol Oncol*, 2007. **24**(8): p. 595-606.

40. Hamidah, A., et al., *Piperacillin-tazobactam plus amikacin as an initial empirical therapy of febrile neutropenia in paediatric cancer patients*. Singapore Med J, 2008. **49**(1): p. 26-30.
41. Simon, A., et al., *Piperacillin-tazobactam in pediatric cancer patients younger than 25 months: a retrospective multicenter survey*. Eur J Clin Microbiol Infect Dis, 2007. **26**(11): p. 801-6.
42. Vidal, L., et al., *Oral versus intravenous antibiotic treatment for febrile neutropenia in cancer patients*. Cochrane Database Syst Rev, 2004(4): p. CD003992.
43. Shahid, S.K., *Efficacy and safety of cefepime in late-onset ventilator-associated pneumonia in infants: a pilot randomized and controlled study*. Ann Trop Med Parasitol, 2008. **102**(1): p. 63-71.
44. Alvarez-Lerma, F., et al., *Efficacy and tolerability of piperacillin/tazobactam versus ceftazidime in association with amikacin for treating nosocomial pneumonia in intensive care patients: a prospective randomized multicenter trial*. Intensive Care Med, 2001. **27**(3): p. 493-502.
45. Schmitt, D.V., et al., *Piperacillin/tazobactam vs imipenem/cilastatin in the treatment of nosocomial pneumonia--a double blind prospective multicentre study*. Infection, 2006. **34**(3): p. 127-34.
46. Zar, H.J. and M.F. Cotton, *Nosocomial pneumonia in pediatric patients: practical problems and rational solutions*. Paediatr Drugs, 2002. **4**(2): p. 73-83.
47. Arguedas, A., et al., *An open, multicenter clinical trial of piperacillin/tazobactam in the treatment of pediatric patients with intra-abdominal infections*. J Chemother, 1996. **8**(2): p. 130-6.
48. Tunkel, A.R., et al., *Practice guidelines for the management of bacterial meningitis*. Clin Infect Dis, 2004. **39**(9): p. 1267-84.
49. Mofenson L.M, et al., *Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America*. MMWR 53(RR-14), 2004: p. 1-92.
50. Warner, J.M., et al., *Melioidosis in a rural community of Western Province, Papua New Guinea*. Trans R Soc Trop Med Hyg, 2007. **101**(8): p. 809-13.
51. Wuthiekanun, V. and S.J. Peacock, *Management of melioidosis*. Expert Rev Anti Infect Ther, 2006. **4**(3): p. 445-55.
52. Lumbiganon, P., N. Chotechuangnirun, and P. Kosalaraksa, *Clinical experience with treatment of melioidosis in children*. Pediatr Infect Dis J, 2004. **23**(12): p. 1165-6.
53. McCarty, J.M., et al., *Comparison of piperacillin alone versus piperacillin plus tobramycin for treatment of respiratory infections in children with cystic fibrosis*. Pediatr Pulmonol, 1988. **4**(4): p. 201-4.
54. Reed, M.D., et al., *Therapeutic evaluation of piperacillin for acute pulmonary exacerbations in cystic fibrosis*. Pediatr Pulmonol, 1987. **3**(2): p. 101-9.
55. Ellis, J.M., J.L. Kutti, and D.P. Nicolau, *Use of Monte Carlo simulation to assess the pharmacodynamics of beta-lactams against Pseudomonas aeruginosa infections in children: a report from the OPTAMA program*. Clin Ther, 2005. **27**(11): p. 1820-30.

Table 1 Studies included in the Cochrane review on oral antimicrobial therapy in cystic fibrosis

| Study | Design | Treatment for | Sample | Interventions |
|---|--|------------------------------|--|--|
| Hodson 1987 Single centre. UK B – Unclear | RCT Aged 16 and over | exacerbations pulmonary | 20 randomly allocated to each group | 3 times a day for 10 days. 1. Azlocillin (5g) plus gentamicin (80mg) both given IV 2. ciprofloxacin (500mg) given orally |
| Jensen 1987 Single centre Denmark B – Unclear | Double-blind RCT Age over 18 yrs Cross over | Chronic infection | 14 in initial ciprofloxacin group and 12 in initial ofloxacin group. 24 received ciprofloxacin and 23 received ofloxacin | For 14 days bd. 3-month washout. 1. ciprofloxacin (750mg) with ofloxacin placebo 2. ofloxacin (400mg) plus CPX placebo |
| Richard 1997 Multi centre 9 countries A – Adequate | RCT Minimum age of 5 years Mean age in cipro group: 10.2 years | exacerbation pulmonary | 108 people randomised (55 to oral Ciprofloxacin and 53 to parenteral combination therapy). | Treatment for 14 days. 1. Oral ciprofloxacin (15mg/kg bd) 2. IV ceftazidime plus tobramycin (50mg/kg tds, 3mg/kg tds). dosage adjusted based on plasma conc. |
| Schaad 1997 Single centre Switzerland B – Unclear | RCT Age: 8 to 25 years | Exacerbations and chronic | 22 maintenance treatment with Ciprofloxacin 23 combination | 2-week IV ceftazidime (300 mg/kg/day) and amikacin (36 mg/kg/day) and bd inhalation of amikacin in all Patients who responded randomised to a 3-month period of OP therapy 1. Oral ciprofloxacin (30 mg/kg/day) 2. Oral ciprofloxacin and amikacin inhalation |

| Study | Design | Treatment for | Sample | Interventions |
|---|--|------------------------|-----------------------------|--|
| Sheldon 1993 UK A Adequate | Double-blind RCT over 18 years of age | Chronic infection | 40 randomised. 31 completed | 1. Ciprofloxacin(500 mg) tds 2. Placebo for 10 days every 3 months for 4 courses |
| Wang 1988 Single centre USA B – Unclear | RCT Over 18 years of age. | exacerbation pulmonary | 23 people randomised | Treatment for 2 weeks 1. Ciprofloxacin 750 mg bd 2. IV tobramycin plus ticarcillin 3. IV tobramycin plus azlocillin |