

Antibiotics for pulmonary exacerbations

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### Background

Respiratory disease is the major cause of mortality and morbidity in cystic fibrosis (CF). Recurrent infection, in particular by *Pseudomonas aeruginosa* (PA), is the main feature of the lung involvement in CF. Life expectancy of people with CF has increased dramatically in the last 40 years. One of the major reasons for this increase is the mounting use of antibiotics to treat chest exacerbations caused by bacterial infections.

Pulmonary exacerbations (PE) have been considered as a high risk factor for morbidity and are constantly present as an important factor in survivorship models in CF. Observational studies show that PE are responsible for an accelerated decline in lung function and, particularly, USA and Canada CF registries show that a significant proportion of patients experiencing a PE, also when treated with intravenous (IV) antibiotics, do not recover lung function to a point prior to the PE; that a substantial proportion of morbidity in CF is associated with seasonality and that there is an association of female gender with high rates of hospitalization for PE.

An assumption underlying a cornerstone of CF care is that PE are associated with bacterial infection leading to the conclusion that IV antibiotics is the more appropriate treatment.

For these reasons, reduced exacerbation rates and rates of respiratory hospitalizations are usually primary endpoints in the studies evaluating the effect of new drugs (i.e. CFTR modulators).

Administration of IV antibiotic therapy for a period of around two weeks is the standard practice for treatment of pulmonary infections in most CF centres, although significant variation exists in the treatment and monitoring of pulmonary exacerbations across Cystic Fibrosis Foundation-accredited care centers ([Cogen JD, 2017](#)).

PE in children with CF are also frequently treated in the outpatient setting with oral antibiotics. Recently, US researchers showed that the treatment of PE with oral antibiotics was associated with measurable improvements in patient reported outcomes, lung function, bacterial density and sputum inflammatory markers ([Hoppe JE, 2018](#)).

PE in CF were comprehensively reviewed in a series of articles published on Thorax ([Goss CH, 2007](#), [Bell SC, 2007](#), [Smyth A, 2008](#)). Reviews examining peculiarities of PE in paediatric patients with CF were also published ([Waters V, 2015](#), [Waters V, 2016](#)).

### Issues

Although administration of IV antibiotic therapy is the standard practice for treatment of pulmonary infections in most CF centres, it is important to **establish if IV antibiotics for the treatment of PE in CF patients improve short- and long-term clinical outcomes**. **Choice of antibiotic, and use of single or combined therapy** are controversial areas in the treatment of respiratory infection in cystic fibrosis (CF). Advantages of combination therapy include wider range of modes of action, possible synergy and reduction of resistant organisms; advantages of monotherapy include lower cost, ease of administration and reduction of drug-related toxicity. To assess the effectiveness of single compared to combination intravenous antibiotic therapy for treating people with CF is reasonably relevant.

To compare antibiotic therapy based on conventional **antimicrobial susceptibility** testing to antibiotic therapy based on combination antimicrobial susceptibility testing in the treatment of acute pulmonary exacerbations in people with CF and chronic infection with PA.

To compare **biofilm antimicrobial susceptibility** testing-driven therapy to conventional antimicrobial susceptibility testing-driven therapy in the treatment of PA infection in people with CF. (protocol)

The optimal **duration of intravenous antibiotic therapy** is not clearly defined. Individuals usually receive intravenous antibiotics for 14 days, but treatment may range from 10 to 21 days. A shorter duration of antibiotic treatment could determine inadequate clearance of infection, leading to further lung damage. Prolonged courses of intravenous antibiotics are expensive and inconvenient and the incidence of allergic reactions to antibiotics also increases with prolonged courses. The use of aminoglycosides requires frequent monitoring to avoid some of their side effects. However, some organisms which infect people with CF are known to be multi-resistant to antibiotics, and may require a longer course of treatment.

Recurrent endobronchial infection in cystic fibrosis (CF) requires treatment with intravenous antibiotics for several weeks usually in hospital, affecting health costs and quality of life for patients and their families. To determine whether **home intravenous antibiotic therapy** in CF is as effective as inpatient intravenous antibiotic therapy and if it is preferred by individuals or families or both.

**Percutaneous long lines (long intravenous lines) and short intravenous lines (also termed cannulae)** are both used to deliver intravenous antibiotics to treat respiratory exacerbations in cystic fibrosis. The perceived advantage of a long intravenous line is a greater duration of line function, which has to be balanced against a technically more challenging insertion procedure, and the possibility of more discomfort on insertion. To compare long intravenous lines with short intravenous lines in people with cystic fibrosis receiving intravenous antibiotics, in terms of lifespan of the line, ease of insertion, complication rates of the line and patient satisfaction will help patients and clinicians to choose between devices.

Finally, **the use of single or combination therapy and the modality of administration** (continuous versus multiple daily

administration for beta-lactams and once vs multiple administrations for aminoglycoside) are also matter for study.

## What is known

### Intravenous Antibiotics For The Treatment Of PE In CF Patients Improve Short-Term And Long-Term Clinical Outcomes

PE have been long treated with antibiotics and this is currently the recommendation ([Doring G. 2012](#), [Flume PA. 2009](#)).

A CDSR ([Hurley MN. 2015](#)) observed that the quality of evidence comparing intravenous antibiotics with placebo is poor. No specific antibiotic combination could be considered to be superior to any other, and neither was there evidence showing that the intravenous route is superior to the inhaled or oral routes. There remains a need to understand host-bacteria interactions and in particular to understand why many people fail to fully respond to treatment.

### Choice Of Antibiotic And Antimicrobial Susceptibility

One CDSR ([Smith S. 2020](#)) examined the question of choosing antibiotics based on combination antimicrobial susceptibility testing compared to choosing antibiotics based on conventional antimicrobial susceptibility testing.

Another CDSR ([Smith S. 2020](#)) examined the issue of comparing biofilm antimicrobial susceptibility testing-driven therapy to conventional antimicrobial susceptibility testing-driven therapy in the treatment of PA infection in people with CF.

There is insufficient evidence to determine the effect of choosing antibiotics based on combination antimicrobial susceptibility testing compared to choosing antibiotics based on conventional antimicrobial susceptibility testing in the treatment of acute pulmonary exacerbations and chronic infection in CF people with PA. Equally, the current evidence shows that there is insufficient evidence to recommend choosing antibiotics based on biofilm antimicrobial susceptibility testing rather than conventional antimicrobial susceptibility testing in the treatment of PA pulmonary infections in CF patients.

One further CDSR ([Jain K. 2016](#)) reviewed the evidence about whether to use samples obtained by bronchoscopy when deciding how to treat lung infections in people with CF. Unfortunately the evidence was very scarce. This review was limited to a single, well designed RCT ([Wainwright CE. 2011](#)); it showed no clear evidence to support the routine use of bronchoalveolar lavage for the diagnosis and management of pulmonary infection in pre-school children with CF compared to the standard practice of providing treatment based on results of oropharyngeal culture and clinical symptoms. No evidence was available for adult and adolescent populations.

A review on this topic is also available ([Lim SZ. 2015](#)).

A systematic review of 20 primary published articles on this issue concluded that there is little evidence that antimicrobial susceptibility testing (AST) predicts the clinical outcome of CF antimicrobial treatment, suggesting a need for careful consideration of current AST use by the CF community. ([Somayaji R. 2019](#))

A recent study examined associations between antimicrobial susceptibility testing (AST) and antimicrobial switching during PEx treatment and time and occurrence of next PEx as treatment outcomes. AST was associated with both increased probability of antimicrobial regimen change and increased PEx hazard. There was no evidence that antimicrobial regimen change was associated with clinical benefit as assessed by time to next PEx. However, these results indicate residual indication bias remained after adjustment for available disease covariates. ([Cogen JD. 2019](#))

A recent review describes how interspecies interactions within the lung microbiome might influence the outcome of antibiotic treatment targeted at common CF pathogens ([Vandeplassche E. 2019](#)).

### Duration Of Intravenous Antibiotic Therapy

The duration of a intravenous therapy course to treat chest exacerbations varies between 10 and 21 days of antibiotics, evaluating improvement of several parameters (pulmonary function and oxygen saturation returning to pre-exacerbation levels, weight increase, normalisation or significant falls in inflammatory markers, improved well-being and clinical symptomatology scores). Shorter duration of antibiotic treatment could increase the risk of inadequate clearance of infection, leading to further lung damage. Prolonged courses of intravenous antibiotics are expensive, tedious and are associated to increased incidence of allergic reactions to antibiotics and risks of side effects. One review ([Sutton KM. 2016](#)) and one CDSR ([Abbott L. 2019](#)) examine this topic. In particular, the Cochrane review concludes that there are no clear guidelines on the optimum duration of intravenous antibiotic treatment. Duration of treatment is currently based on unit policies and response to treatment. Shorter duration of treatment should improve quality of life and adherence, result in a reduced incidence of drug reactions and be less costly. However, the shorter duration may not be sufficient to clear a chest infection and may result in an early recurrence of an exacerbation. There is a relevant need for a multicentre, randomised controlled trial comparing different durations of intravenous antibiotic treatment as it has important clinical and financial implications.

Recently, US researchers combined a survey of CF stakeholders with retrospective analyses of a recent observational study of CF PEx to design a multicenter, randomized, prospective study (STOP2) comparing the efficacy and safety of different durations of IV antibiotics for PEx to meet the needs of people with CF and their caregivers ([Heltshe SL. 2018](#)). During PE FEV<sub>1</sub>% predicted and symptom responses at 7-10days of IV antibiotics identified two distinct groups: early robust responders (ERR) who subsequently experienced greater FEV<sub>1</sub> improvements compared to non-ERR (NERR). In conclusion, the authors hypothesize that 10 days IV antibiotic treatment (ERR-10) is as safe as and not clinically inferior (in terms of lung function) to 14 days (ERR-14). Moreover they hypothesize that 21 days (NERR-21) is clinically superior (in terms of lung function) and safe, compared to 14 days (NERR-14) IV antibiotic treatment. So, an adequate duration of therapy could be 10 vs. 14days for ERR, 14 vs. 21days for NERR.

Nicholson et al. [[Nicholson TT. 2021](#)] presents a systematic review of exacerbation literature, spanning all years up to 2016, just before the landmark STOP2 study. This systematic review focuses on how duration of antibiotic treatment for exacerbations impacts outcomes including lung function (FEV<sub>1</sub>), peripheral white cell count and C-reactive protein (CRP). Overall, the systematic review identifies that outcomes after treatment for 10-12 days were similar in outcomes to treatment for longer (13–15 days), which supports the results of the

STOP2 study. Longer duration of antibiotic treatment was associated with greater improvements in CRP although CRP was higher at onset of exacerbation in the groups treated for a shorter time.

Further updates from the STOP2 study have been published recently. Mean ppFEV<sub>1</sub> change was 12.8 and 13.4 for 10 and 14 days, respectively, a  $\approx 0.65$  difference (95% CI [ $\approx 3.3$  to 2.0]), excluding the predefined noninferiority margin. The 21- and 14-day arms experienced 3.3 and 3.4 mean ppFEV<sub>1</sub> changes, a difference of  $\approx 0.10$  ( $\approx 1.3$  to 1.1). Secondary endpoints and sensitivity analyses were supportive. In conclusion, among adults with CF with early treatment improvement during exacerbation, ppFEV<sub>1</sub> after 10 days of intravenous antimicrobials is not inferior to 14 days. For those with less improvement after one week, 21 days is not superior to 14 days ([Goss CH, 2021](#)).

### Home Vs Hospital Care

Home intravenous (IV) therapy in CF is a possible response to both increasing demand for hospital beds, and the need for treatment to interfere as little as possible with the individual's normal lifestyle and quality of life. Home IV therapy may also cut costs. It is important to determine whether home IV antibiotic therapy in CF is as effective as inpatient IV antibiotic therapy, for exacerbation of lung disease and if home therapy is preferred by individuals and/or families to inpatient IV antibiotic therapy.

One CDSR ([Balaguer A, 2015](#)) examines this topic. The current evidence is too limited to draw conclusions for practice. Only one RCT, involving 17 patients, compared intravenous antibiotic treatment in hospital to treatment at home ([Wolter JM, 1997](#)). No differences for clinical outcomes, adverse events, or complications linked to intravenous treatment was evident. Home therapy was more tiring and the treatment was considered more difficult to master. Home therapy was cheaper for families and the hospital. In the short term, home therapy is associated with less social disruption and no serious adverse events. The decision in favour of this option must be made on an individual basis. Home intravenous antibiotic therapy in patients with cystic fibrosis was estimated to be a feasible alternative to receiving therapy in hospital. The costs of home therapy were usually lower than those of inpatients settings ([Donati MA, 1987](#)). Hospital treatment for respiratory exacerbations in patients with CF was both more effective and more costly than home treatment. Although there was no clinical compromise associated with home therapy, there were advantages and disadvantages in terms of quality of life. Hospital patients were estimated to present better results in terms of fatigue, mastery and total scores, while home patients were estimated to fare better in terms of family and personal life, sleep and total disruption.

The impact of home vs hospital care has been re-evaluated in a multicenter, randomized, prospective study (STOP2). The researchers' hypothesis was that participants treated at home would have less improvement in lung function compared to those treated in the hospital. In fact, mean (95% CI) ppFEV<sub>1</sub> improvement was significantly ( $p < 0.05$ ) lower for those subjects treated at home only, 5.0 (3.5, 6.5), compared with at home and in the hospital, 7.0 (5.9, 8.1), and in the hospital only, 8.0 (6.7, 9.4). Mean weight ( $p < 0.001$ ) and symptom ( $p < 0.05$ ) changes were significantly smaller for those treated at home only compared to those treated in the hospital only. In conclusion, compared to PEx treatment at home only, treatment in the hospital was associated with greater mean lung function, respiratory symptom, and weight improvements. The limitations of home IV therapy should be addressed in order to optimize outcomes for adults with CF treated at home ([Sanders DB, 2021](#)).

### Single Versus Combination Intravenous Antibiotic Therapy

Choice of antibiotic, single or combined therapy and the duration of treatment are controversial areas in the treatment of infection with IV antibiotics in CF. Current practice showed that monotherapy is now rarely used. Most centres perceive dual or combination IV antibiotic therapy in CF to be more effective than single therapy. It has been suggested that a clinic policy of using monotherapy with a beta-lactam antibiotic may be responsible for the emergence of resistant strains of PA. Use of a single antibiotic (usually beta-lactam alone) would offer advantages because of ease of administration and lower costs.

One CDSR ([Elphick HE, 2016](#)) is available on this topic. Evaluation of the evidence regarding the benefits and risks of single versus combination antibiotic therapy in cystic fibrosis is inconclusive. In particular, side effects of treatment have not been investigated to a sufficient level, and therefore it is not possible to conclude that either treatment choice is safe compared to the other.

VanDevanter et al. ([VanDevanter DR, 2022](#)) retrospectively studied treatment responses for STOP2 PEx treatment trial (NCT02781610) participants with a history of *Pa* infection. Mean lung function and symptom changes from intravenous (IV) antimicrobial treatment start to Visit 2 (7 to 10 days later) were compared between those receiving one, two, and three+ antipseudomonal classes. No lung function or symptom response, odds of retreatment, or future PEx hazard differences were observed by number of antipseudomonal classes administered in primary or sensitivity analyses. In conclusion the authors were unable to identify additional benefit when multiple antipseudomonal classes are used to treat PEx in people with CF and *Pa*.

Limited data exist to inform antibiotic selection among people with cystic fibrosis (CF) with airway infection by multiple CF-related microorganisms. Subjects with CF co-infected with methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* (*Pa*) could benefit by the addition of anti-MRSA antibiotics to antipseudomonal antibiotic treatment for pulmonary exacerbations (PEx). A study analyzing data of the US CFF Registry ([Cogen JD, 2022](#)) retrospectively evaluated the clinical outcomes in children with CF co-infected with MRSA and *Pa*. The study showed that these patients may not benefit from the addition of anti-MRSA antibiotics for PEx treatment. Prospective studies evaluating optimal antibiotic selection strategies for PEx treatment are however needed to optimize clinical outcomes following PEx treatment.

### Percutaneous Long Lines (Long Intravenous Lines) Vs Short Intravenous Lines (Also Termed Cannulae)

IV antibiotics are one of the main therapeutic option for CF lung disease. There are several methods for delivering IV antibiotics. A short IV line (also termed a cannula) is a short flexible plastic tube inserted over a hollow needle which protrudes just beyond the tip of the plastic tube. A long IV line is a variant of this, in which the vein is punctured with a needle, and a longer (several centimetres) flexible hollow tube is inserted through the needle into the vein, following which the needle is removed. These are also inserted into peripheral veins. Insertion of short and long IV lines are typically done at the participant's bedside. Long IV lines can be of varying lengths, the midline, a peripheral line, terminating in axillary or subclavian vein and the PICCs (Peripherally Inserted Central Catheters), terminating in a central vein.

The hypotheses to verify are:

- to compare long IV lines with short IV lines in people with CF receiving IV antibiotics, in terms of lifespan of the line, ease of insertion, complication rates of the line and patient satisfaction;
- to compare different types of long IV lines;
- to assess if aids to insertion (i.e. with or without ultrasound guidance) impact upon the successful insertion rate.

One CDSR ([Prayle AP, 2010](#)) is available. Long IV lines for administering IV antibiotics in CF appear superior to short IV lines in terms of lifespan of the line and patient satisfaction. Long IV lines are therefore a useful and effective intervention to deliver antibiotic therapy. Studies do not have statistical power to detect a difference in the rates of serious complications such as bacteraemia. There is no clear evidence of superiority of one line over others in terms of lifespan of the line, patient satisfaction or complication rate. The choice of long line is largely determined by operator and patient preference.

#### **Totally Implantable Vascular Access Devices (TIVAD)**

TIVAD have many advantages when compared to external indwelling catheters: there is no external portion attached when the device is not in use so physical activity is not limited; long-term maintenance is relatively easy and is done by flushing with heparinized saline once every four to six weeks.

The hypotheses to verify are:

- if TIVAD are a safe and effective route for providing venous access for intermittent administration of antibiotics in people with CF;
- if it is possible to reduce complications of TIVAD (e.g. anticoagulants to reduce the risk of thrombosis).

One CDSR ([A-Rahman AKM, 2012](#)) is available. One RCT about complications of TIVAD has been recently completed, but no publication is available. No conclusions can be made about the use of TIVAD in people with CF from the literature currently available. Clinicians must balance potential benefit against the possible risk of complications in each case.

#### **Inhaled Antibiotics**

The practice of prescribing inhaled antibiotics for many years used to suppress chronic infection in people with CF is widespread. There is evidence that inhaled antibiotic treatment of chronic infection is of some benefit in terms of improvement in lung function and reduction in exacerbations of respiratory infection. In practice, inhaled antibiotics are often used to treat pulmonary exacerbations as recently described in an observational study by the Epidemiologic Study of Cystic Fibrosis ([Wagener JS, 2012](#)). It is important to determine if treatment of pulmonary exacerbations with inhaled antibiotics in people with CF improves their quality of life, reduces time off school or work and improves their long-term survival.

One CDSR ([Smith S, 2018](#)) is available. There is little useful high-level evidence to judge the effectiveness of inhaled antibiotics for the treatment of PE in people with CF. The included trials were not sufficiently powered to achieve their goals. Hence, the review is unable to demonstrate whether one treatment is superior to the other or not. Further research is needed to establish whether inhaled tobramycin may be used as an alternative to intravenous tobramycin for some pulmonary exacerbations.

#### **Modality Of Administration Of Intravenous Antibiotics**

##### *AMINOGLYCOSIDES*

Aminoglycosides demonstrate concentration dependent killing and the post-antibiotic effect; it means that the bactericidal action of aminoglycosides is related to the peak concentration of antibiotic achieved. Greater bactericidal effect occurs at concentrations exceeding the minimum inhibitory concentration (MIC). The post-antibiotic effect is a phenomenon in which the bactericidal action of the aminoglycoside continues even after the antibiotic has been cleared and its concentration has fallen below the MIC. These pharmacological properties suggest that aminoglycosides could be given in higher concentrations with an extended dosing interval. People with CF are vulnerable to cumulative side effects from antibiotics as they receive recurrent and prolonged courses of treatment, so the less ototoxic and nephrotoxic strategy of administration is a relevant matter. Once-daily aminoglycoside dosing has major advantages to people with CF and their families, especially if they receive their antibiotics at home. In addition there are cost implications in reducing the use of consumables and the time taken to prepare and deliver antibiotics.

The hypotheses will be tested that once-daily intravenous aminoglycoside dosing is:

- as effective as multiple-daily dosing (as measured by the change in lung function over a course of antibiotic treatment)
- no more toxic than multiple-daily dosing (as measured by renal and auditory toxicity).

One CDSR ([Bhatt J, 2019](#)) is available on this topic. No difference in efficacy between the two treatment regimens has been demonstrated, though caution is still needed over the effects on renal function in adults. Once-daily aminoglycoside treatment for pulmonary exacerbations of CF may be adopted as it is more convenient for people with CF.

Recently, a review article summarizes the currently available literature and identifies gaps in the literature related to pharmacokinetic parameter goals, aminoglycoside dosing strategies, and methods for monitoring serum aminoglycoside concentrations for treatment of PA in CF ([Ochs MA, 2021](#))

##### *CEFTAZIDIME*

The pharmacodynamics of  $\beta$ -lactam antibiotics is characterized by time-dependent killing, in which antibacterial activity is dependent on the amount of time that the drug concentration is above the minimum inhibitory concentration (MIC) of the bacteria. Continuous infusion administration can achieve time above the MIC for the entire dosing interval, which may be critical for the treatment of multidrug-resistant PA. Intermittent dosing may allow drug concentrations to fall below the MIC of the resistant organism, which would permit bacterial survival and regrowth. Ceftazidime is one of the most used beta – lactam antibiotic.

The hypotheses will be tested that continuous infusion of ceftazidime is:

- as effective as multiple-daily dosing (as measured by the change in lung function over a course of antibiotic treatment)
- no more toxic than multiple-daily dosing

2 well designed RCT were available ([Hubert D. 2009](#); [Riethmuller J. 2009](#)). No difference in efficacy between the two treatment regimens of administration of Ceftazidime (+ once-daily Tobramycin) was demonstrated, though better results were observed in patients harboring resistant isolates of PA.

**Ceftazidime/avibactam** is a new combination which, in vitro, appears to have good activity against Multi-Drug-Resistant strains of *P. aeruginosa* and *B. cepacia* complex. Case and case-series reports are only available ([Spoletini G. 2019](#)).

#### **MEROPENEM**

One RCT is ongoing on population pharmacokinetics of prolonged infusion of Meropenem in CF children.

## **Unresolved questions**

### **Choice Of Antibiotic And Antimicrobial Susceptibility**

A larger, adequately powered, study is needed to determine if the combination of antimicrobial susceptibility testing may be beneficial in people with CF and chronic PA infection. Another point of view in this matter is that antimicrobial susceptibilities determined for bacteria growing as a biofilm (as in the bronchial tree), rather than planktonically, would lead to more reliable antibiotic choices in treating PA exacerbation. There is evidence that biofilm inhibitory concentrations (concentrations of antibiotics that inhibit biofilm growth) for PA are much higher (100 to 1000 times) than the corresponding conventionally determined minimum inhibitory concentrations (MICs) for several classes of antibiotics including  $\beta$ -lactams. Hence, antibiotic susceptibilities based on biofilm-grown PA may lead to different antibiotic choices with potentially improved microbiological and clinical outcomes. A larger, adequately powered, study is needed also on this topic.

### **Percutaneous Long Lines (Long Intravenous Lines) Vs Short Intravenous Lines (Also Termed Cannulae)**

There are numerous percutaneous long IV lines currently marketed for IV access in children and adults. There is a need to compare such devices in order to establish superiority of one device over another, although it is difficult to make a fair comparison between two interventions when the operators tend to have more prior experience with one device before a study commences. Important outcome measures could include proportion of courses of IV antibiotics completed with a single line, number of attempts, number of doses of antibiotic missed per patient and number of procedures per patient. Patient satisfaction as a primary outcome measure should ideally be included.

### **Totally Implantable Vascular Access Devices (Tivad)**

There is nowadays the need for well-designed, adequately-powered, multicentre, RCTs to assess the efficacy and safety of the use of TIVAD in people with CF compared to other means of vascular access, to compare the different types of these devices with each other and to assess strategies to reduce any complications of TIVAD.

## **Keywords**

Bacterial Infections; *Burkholderia cepacia*; Colonization; Exacerbation; *Haemophilus influenzae*; Infection; Pneumonia; *Pseudomonas aeruginosa*; Respiratory Tract Infections; *Staphylococcus aureus*; *Stenotrophomonas Maltophilia*; Aminoglycosides; Anti-Bacterial Agents; Carbapenems; Cephalosporins; Macrolides; Monobactams; Others anti-bacterial agents; Penicillins; Quinolones; Tetracyclines;