Piperacillin - Tazobactam

Newborn use only

2020

<table>
<tr><td>Alert</td><td>The Antimicrobial Stewardship Team has listed this drug under the following categories: Restricted.</td></tr>
<tr><td>Indication</td><td>Therapy of non-CNS systemic infections, necrotising enterocolitis and intra-abdominal infections caused by susceptible Gram positive and Gram negative bacteria including anaerobes and many Enterobacterales and Pseudomonas spp.(1)
Susceptibility of coagulase-negative staphylococci (CONS) is generally not tested though oxacillin-resistant CONS should be considered resistant and piperacillin-tazobactam should not be used as first-line for suspected CONS sepsis.(2)</td></tr>
<tr><td>Action</td><td>β-lactam/β-lactamase inhibitor combination with a broad spectrum of antibacterial activity encompassing Gram-positive and Gram-negative aerobic bacteria and anaerobic bacteria, including many pathogens producing β-lactamases.(1) Piperacillin component is a semi synthetic penicillin that inhibits septum and cell wall synthesis of susceptible bacteria. Tazobactam is a beta lactamase inhibitor that enhances the antibiotic spectrum of piperacillin.</td></tr>
<tr><td>Drug type</td><td>Antibiotic – ureidopenicillin and beta-lactamase inhibitor.</td></tr>
<tr><td>Trade name</td><td>Piperacillin/Tazobactam Kabi, Tazocin EF, PiperTaz, Piptaz, PipTaz-AFT, Tazopip</td></tr>
<tr><td>Presentation</td><td>4.5 g vial (4 g piperacillin and 0.5 g tazobactam).</td></tr>
<tr><td>Dose</td><td>Dose based on piperacillin component (3, 4)
<table>
<tr><th>Corrected Gestational Age/Postmenstrual Age</th><th>Dose</th><th>Interval</th></tr>
<tr><td>$< 30^{+0}$ weeks</td><td>100 mg/kg/dose</td><td>8 hourly</td></tr>
<tr><td>30^{+0}–35^{+6} weeks</td><td>80 mg /kg/dose</td><td>6 hourly</td></tr>
<tr><td>$\geq 36^{+0}$ weeks*</td><td>80 mg/kg/dose</td><td>6 hourly</td></tr>
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*Consider 4 hourly dosing if culture-proven sepsis in this group</td></tr>
<tr><td>Dose adjustment</td><td>Therapeutic hypothermia – Evidence is lacking to guide dose adjustment.
ECMO – While standard dosing may be adequate for susceptible organisms, studies in adults have shown poor PK target attainment for the directed therapy of Pseudomonas aeruginosa. Seek infectious diseases consultant advice(5, 6)
Renal impairment – Use with caution. Concurrent use with vancomycin has been suggested to be associated with an increased incidence of acute kidney injury in adults and children but unclear in neonates. (7-11)
Hepatic impairment – No dose adjustment is required.</td></tr>
<tr><td>Maximum dose</td><td></td></tr>
<tr><td>Total cumulative dose</td><td></td></tr>
<tr><td>Route</td><td>IV</td></tr>
<tr><td>Preparation</td><td>Add 17 mL water for injection to the 4.5 g vial to make a concentration of 200 mg/mL of piperacillin equivalent solution.
FURTHER DILUTE
Draw up 2 mL (400 mg of piperacillin equivalent) and add 8 mL of sodium chloride 0.9% to make a final volume of 10 mL with a final concentration of 40 mg/mL of piperacillin equivalent.</td></tr>
<tr><td>Administration</td><td>IV infusion over 30 minutes. (3)</td></tr>
<tr><td>Monitoring</td><td>Complete blood count, electrolytes, renal and hepatic function during prolonged treatment (> 10 days).</td></tr>
<tr><td>Contraindications</td><td>Hypersensitivity to any of the penicillins and/or cephalosporins or beta-lactamase inhibitors.</td></tr>
<tr><td>Precautions</td><td>Prolonged therapy increases risk of leucopenia, neutropenia and thrombocytopenia. High doses may lead to hypernatraemia (owing to sodium content of preparations) (12)</td></tr>
<tr><td>Drug interactions</td><td>May potentially:
Enhance the nephrotoxic effect of vancomycin.
Affect the blood coagulation system when given with high doses of heparin and oral anticoagulants.
Increase the serum concentration of flucloxacillin.
Increase the prolongation of the neuromuscular blockade of vecuronium.</td></tr>
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Adverse reactions	Generally well tolerated. Hypersensitivity reactions can occur. Rash (maculopapular), phlebitis, thrombophlebitis. Diarrhoea, nausea, vomiting, stomatitis and pseudomembranous colitis (*Clostridium difficile*). Black tongue, fever, anaphylactic shock, angioedema, bronchospasm. Leucopenia, thrombocytopenia, anaemia. Elevated transaminases. Renal impairment. Hypokalaemia, hypernatraemia, metabolic alkalosis. Candidiasis. High doses may lead to hypernatraemia (owing to sodium content of preparations) Uncommon - Hypotension.
Compatibility	Fluids: Sodium chloride 0.9%, glucose 5%, glucose 10% Y-site: EDTA-free brands only (NOT Tazocin EF): Amino acid solutions, aminophylline, anidulafungin, aztreonam, bivalirudin, buprenorphine, calcium folinate, calcium gluconate monohydrate, clindamycin, dexamethasone, dexmedetomidine, dopamine, fluconazole, furosemide (frusemide), granisetron, heparin sodium, hydrocortisone sodium succinate, hydromorphone, linezolid, magnesium sulfate heptahydrate, methylprednisolone sodium succinate, metoclopramide, metronidazole, morphine sulfate pentahydrate, pethidine, potassium chloride, ranitidine, remifentanil, tigecycline, trimethoprim + sulfamethoxazole, zidovudine. Y-site: Tazocin EF only: No information available.
Incompatibility	Fluids: Albumin, blood products, Hartmann's and alkaline solutions. (AIDH) Y site: Aciclovir, albumin, amikacin, amiodarone, azithromycin, caspofungin, chlorpromazine, ciprofloxacin, dobutamine, droperidol, ganciclovir, gentamicin, glycopyrronium bromide (glycopyrrolate), haloperidol lactate, hydralazine, insulin (short-acting), labetalol, midazolam, mycophenolate mofetil, pentamidine isetionate, promethazine, rocuronium, sodium bicarbonate, thiopentone, tobramycin, tranexamic acid, vecuronium, verapamil.
Stability	Reconstituted solution is stable for 24 hours below 25°C or at 2–8°C. Immediate use is recommended.
Storage	Store vial below 25°C
Excipients	PiperTaz Sandoz, PipTaz AFT and Tazopip are EDTA-free. Contain 2.35 mmol of sodium for each 1 g of piperacillin. PipTaz AFT also contains sodium bicarbonate. Tazocin EF also contains citric acid monohydrate and disodium edetate (EDTA). Contains 2.84 mmol of sodium for each 1 g of piperacillin.
Special comments	Doses here are expressed as the piperacillin component.
Evidence	**Efficacy** A prospective, open-label non-comparative trial by Berger et al in 27 very low birthweight (VLBW) infants ≤1500 g with nosocomial sepsis, necrotising enterocolitis, intra-abdominal infections found that piperacillin-tazobactam is safe and well tolerated with no adverse events considered related to the drug. Clinical efficacy evaluation revealed cure or improvement in 17 patients (63%). Of the 10 patients with unfavorable clinical response, two had growth of pathogens resistant to piperacillin-tazobactam in the blood culture (one with oxacillin resistant Staphylococcus epidermidis and the other with Candida albicans). In one patient with NEC and perforation, surgical treatment was withheld due to the extremely low birth weight and poor general condition of this patient, resulting in death 3 days after beginning of piperacillin/tazobactam treatment. (13) **Dose schedule:** Prospective multicenter non-comparative trial by Cohen-Wolkowiez et al in preterm and term infants of <61 days with suspected systemic infection suggested a Postmenstrual age (PMA)-based dosing (100 mg/kg q 8 h, 80 mg/kg q 6 h, and 80 mg/kg q 4 h for

	PMA of<30, 30 to 35, and 35 to 49 weeks, respectively), to achieve therapeutic target of time above the MIC (≤32mg/liter) for 75% of the dosing interval in 90% of infants. This study also suggested no advantages of prolonged (2−4 hour) infusion over short (over 30 minutes) infusion.(3) While the study recommends 4 hourly dosing for 35−49 weeks gestation, prolonging the interval to 6 hours in this group was also suggested as reasonable particularly for culture negative sepsis as 6-hour regime still attains the target rate in 80% of this group. (3, 4) **ECMO:** A case-control study in adults showed that volume of distribution and clearance was similar compared to non-ECMO patients, but only 40% of adults on ECMO achieved the target exposure for treatment of Pseudomonas aeruginosa when receiving a dose of 4 g every 6 hours. (5, 6) Based on these results, while standard dosing may be adequate for susceptible organisms, an alternate antibiotic such as meropenem has been suggested for serious infections in patients on ECMO. **Combination drugs and acute kidney injury (AKI):** Prospective trials in adults suggest Piperacillin-tazobactam does not cause kidney injury when given as a single agent. (14) Adult meta-analysis using retrospective data suggested that piperacillin-tazobactam and vancomycin combination was associated with AKI, (10) but this remains controversial and further study is required. (9) A recent neonatal multicentre retrospective study evaluating the incidence of AKI found decreased risk of AKI with vacomycin and piperacillin-tazobactam combination, relative to gentamicin + indomethacin. (11) **Safety** Study by Berger et al found no clinical adverse events in VLBW infants, in particular, no cases of phlebitis, rash or stool changes. No long-lasting effect on the intestinal flora was detected. Several mild and transitory laboratory abnormalities including elevated direct bilirubin and other liver enzymes, thrombocytosis and elevated eosinophilic count were noted but none of them required discontinuation of antibiotic therapy.(13) **Pharmacokinetics** It is primarily excreted via kidneys by glomerular filtration and tubular secretion. Therefore, renal impairment may affect drug elimination. Piperacillin-tazobactam has unreliable CNS penetration and should not used for CNS infections (E.g. meningitis)
Practice points	Piperacillin - tazobactam can be safely used for treatment of non-CNS systemic infections, necrotising enterocolitis and intra-abdominal infections in very low birth weight infants.(13) (LOE IV, GOR B) The recommended dose regimen in this formulary is a pragmatic adaptation of the dosing suggested by Cohen-Wolkowiez et al. (3) (LOE IV, GOR B)
References	1. Perry CM, Markham A. Piperacillin/Tazobactam. Drugs. 1999;57(5):805-43. 2. John Jr JF, Davidson R, Low DE. Staphylococcus epidermidis and other coagulase-negative staphylococci. Antimicrobial therapy and vaccines E-Sun Technologies, Pittsburgh, PA. 2010. 3. Cohen-Wolkowiez M, Watt KM, Zhou C, Bloom BT, Poindexter B, Castro L, et al. Developmental pharmacokinetics of piperacillin and tazobactam using plasma and dried blood spots from infants. Antimicrobial agents and chemotherapy. 2014;58(5):2856-65. 4. Salerno S, Hornik CP, Cohen-Wolkowiez M, Smith PB, Ku LC, Kelly MS, et al. Use of population pharmacokinetics and electronic health records to assess piperacillin-tazobactam safety in infants. The Pediatric infectious disease journal. 2017;36(9):855. 5. Donadello K, Antonucci E, Cristallini S, Roberts JA, Beumier M, Scolletta S, et al. β-Lactam pharmacokinetics during extracorporeal membrane oxygenation therapy: a case–control study. International journal of antimicrobial agents. 2015;45(3):278-82. 6. Sherwin J, Heath T, Watt K. Pharmacokinetics and dosing of anti-infective drugs in patients on extracorporeal membrane oxygenation: a review of the current literature. Clinical therapeutics. 2016;38(9):1976-94. 7. MIMS. Piperacillin/Tazobactam. (Accessed on 5 November 2020).

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